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## OBSTETRICS AND GYNECOLOGY

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### OBSTETRICS AND GYNECOLOGY TODAY\*

#### President's Address

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EVERYBODY, but everybody, knows more about Obstetrics and Gynecology than the obstetrician-gynecologist himself.

The Anesthetist tells us all about infant resuscitation and conduction anesthesia, which many of us use extensively.

The Pediatrician knows all about the proper care of babies. He is ever ready to advise about resuscitation, and thinks he could do a better job than we do.

The Internist knows more about most things than we do. It would be difficult to enumerate all the subjects about which he knows most. Sometimes, I think he should be the one to write textbooks of obstetrics.

The Endocrinologist believes he should be invoked for all menstrual aberrations and problems of intersexuality. Without his blessing, he is sure no such patient can be properly treated.

The Urologist knows more about pyelonephritis of pregnancy and the repair of urinary tract fistulas than we do. Some of them feel this way about congenital anomalies of the female reproductive tract.

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The General Surgeon is a little doubtful of our knowledge of surgical conditions within the abdomen, and veils rather thinly his opinion of our technical abilities.

The Radiologist, by virtue of dealing with ionizing radiation, knows more about the treatment of female genital cancer than we do.

Recently, the Geneticist emphasized the possible harm of radiation-induced mutations to unborn children many generations in the future. Together with the Pathologist and the Radiologist he has succeeded in disseminating widely the belief that diagnostic x-ray, done purely for obstetric reasons, is out of place in the modern world.

The Basic Scientist, in whatever field, believes we are incapable of fundamental research. Not only does he know more about it than we do, but also he is skeptical of anything we might happen to produce even in the clinical field.

The idea that our professional colleagues know so much more about what is good for our patients, and for obstetrics and gynecology, than we do reached its zenith in a news item published in the *Chicago Tribune* of May 4, 1958, entitled, "Embryology Specialty for Doctors Urged." The heading was in bold-faced letters more than a quarter of an inch high. It seems that a Cincinnati professor of research pediatrics proposed creation of a new medical specialty dedicated to the unborn child. He was quoted as saying that, "... the proposed new medical specialists be given knowledge of gynecology, obstetrics, embryology, and genetics, and that prevention, and not repair, be the chief objective."

What about those in ancillary fields, the Social Workers, Public Health and Hospital Administrators, and Nurses? Do they know more about obstetrics and gynecology than we do? From the rather free way they tend to advise us, I suspect they do. Certainly, we have all heard of the "multidisciplined" approach to the obstetric problem. Those who are not sure they possess superior knowledge at least wish somehow to get into the act.

The Patient, herself, frequently attempts to prescribe locale and methodology. In the last analysis, she is always capable of reminding us that we never had a baby.

I believe these attitudes of superiority toward us and our specialty exist in varying degree and form throughout the nation. One hundred and seventy million Americans cannot all be wrong. Therefore, there must be some justification for their attitudes and beliefs. Could it be that the doctor of medicine, both the general practitioner and the specialist, is not giving satisfaction to the obstetric and gynecologic patient?

Some idea of what the patient thinks may be obtained from an article by a mother and professional writer, Joan Beek, which was presented at the Seventh American Congress on Maternal Care. The opening paragraph states, "Young mothers, generally, are well satisfied with the physical care they receive during pregnancy and childbirth. But they have deep-felt needs for information and emotional support which are not being met—by their physicians, by the hospitals in which their babies are born, or by the nurses they encounter." The



rest of the article clearly and forcefully documents the various deficits in obstetric care as seen by the young mother. In conclusion, the last paragraph, quoted in part, says, "If doctors aren't willing—or feel they can't afford the time—to do this, they must make it clear they have no intention of living up to their current billing as the focal point of maternity care and limit their field to the handling of medical emergencies."

To this audience, there is little of newness in the foregoing paragraphs. Nevertheless, it deserves emphasis, because I think we all will agree that in general doctors are not satisfying their maternity patients. Specialists are no different from generalists in this regard.

Interestingly, it is in the field of obstetrics, rather than in gynecology, where we are especially criticized for not meeting the intellectual and emotional needs of the patient. Through the public prints the maternity patient is led to expect certain information and care, and hopes to receive some of the emotional support which requires just a little bit of extra time and attention from her physician. The expectant mother, particularly she who engages a specialist, enjoys consuming curiosity concerning the reproductive process. Who, she reasons, is better able to tell her what she wants to know than her doctor. In addition, the emotionally supercharged atmosphere always surrounding the reproductive process potentiates and magnifies feelings unlikely to come to the surface in other less tense circumstances. In the field of gynecology, there is normally no such supercharge, and we meet no more than the current dissatisfaction commonly leveled at the entire medical profession.

If the basic premise be accepted that perhaps we are not all we should be, then we must inquire why, since analysis must precede remedial action. Why do others impugn our knowledge, force advice upon us, and often insist on taking over—except in the delivery room at three o'clock in the morning? It seems to me the answers fall into two broad groups: (1) Our specialty is so young there has been insufficient time to unify our objectives. (2) Our level of professional erudition generally leaves something to be desired.

Our friend and colleague, Daniel G. Morton, says, "We are a motley crew, you and I. Some of us are obstetricians, some are gynecologists, and some are both. A few of us are infertility experts almost exclusively, and a number of us are really female endocrinologists. Others of us emphasize the surgical aspects of our specialty while a few of us scarcely touch the knife. Some of us are cancer specialists and a few of us are pathologists. We have arrived at our respective accomplishments by many and devious routes; we are the products of all manner of different training programs."

It seems to me we are a motley crew because we have developed rapidly, deviously, and without plan. There has been little time to agree among ourselves or to formalize programs, except in certain centers. So lacking are we in agreement that there remain within our ranks those who believe it is beyond one man's capacity to encompass knowledge and skills in both obstetrics and gynecology. This view is inconceivable to me, because in my lifetime capacity

as a professional teacher and trainer of combined obstetric-gynecologic specialists, I have seen many average young physicians become knowledgeable and skillful in both fields. At this point it may be worth while to digress for a few sentences.

There is nothing about unilateral training which confers the right to practice the other specialty without additional and equivalent training. Those of you who are contemporaneous with me will instantly call to mind several sorry instances of men in high places who tried unsuccessfully to do just this. Management of complicated obstetric patients requires rare judgment, seldom acquired without careful training under adequate tutelage, and certainly never achieved unless the requisite time has been spent in the obstetric clinics, wards, and delivery rooms. By the same token, possession of obstetric knowledge and judgment does not grant the possessor the right to "barge" into the gynecologic operating room and pretend to be a trained surgeon. The motor nerves and the muscles they supply require long periods of training for proficiency in operating, to say nothing of the time necessary to acquire requisite knowledge of the basic pathology. Now that the combination of obstetrics and gynecology is generally accepted, especially in the medical schools of the nation, I venture to express the hope that unilaterally trained men of my age will join with us in furthering the future of the combined specialty, even though they may expect little personal gain by doing so.

Before this diversion, I proposed to document our relative adolescence by a brief airplane flight, skimming over the highlights of history. The midwife controlled obstetric practice from the beginning of recorded history until about 250 years ago. The male animal was unwelcome in the lying-in chamber except in emergency, when his contribution probably was aggressiveness rather than knowledge and skill. The Obstetric Revolution, set in motion by the introduction of the forceps, displaced the midwife and upset age-old customs. Obviously, this did not happen quickly, or without a struggle. America did not take so kindly to the innovation, or as rapidly as did Europe, and the male midwife did not begin to emerge in this country until the end of the last century. Surgical gynecology, with its origins almost entirely in America, was unable to develop until the last quarter of the nineteenth century, after the introduction of anesthesia, hemostasis, and asepsis. In fact, it was less than seventy years ago that definitive cure of cancer of the cervix, rather than palliation, appeared for the first time in the history of the world.

The number of professed or trained obstetric-gynecologic specialists in the United States at the end of the second decade of the present century probably did not exceed 500, although there are virtually no early records available to substantiate or controvert this point. Today it is currently estimated that at least 7,500 physicians confine their practice to obstetrics or gynecology.

During the third decade of this century more was discovered concerning the physiology of the female reproductive tract than was known in all of previous history. Whether or not this stimulated movement of young physicians into our specialty cannot be stated. Nevertheless, during the 1920's the number

of physicians interested in and practicing obstetrics or gynecology increased so that by the end of the decade a need became apparent. The incorporation in 1930 of the American Board of Obstetrics and Gynecology marks the date of the formal beginning of our combined specialty. Today there are more than 5,000 diplomates of the "Board."

A brief review of the residency situation will serve further to document our youthfulness. My generation was among the first to be able to secure formalized, bilateral training. Even so, when I sought a combined residency, those available and acceptable could be counted on the fingers of one hand. In other words, combined training at that time was available only to a few. In consequence, some took obstetric residencies in one place and gynecologic residencies elsewhere. Others carved out their training by visiting and residing briefly, or in informal fashion, in various medical centers. Others sought preceptors. Still others went into practice, slanted their interests toward obstetrics, and trained themselves on the job. No wonder "we are a motley crew." Currently there are more than 2,000 residents in training in our field. Many of these men either receive unilateral training, usually in obstetrics, or their residencies are approved for only one year. Probably not more than half of the 2,000 residents serving in "approved" residencies receive training approaching optimum. Our relative youth is certainly apparent in this area. The very quantity of the residencies which sprang up like weeds during the last two and a half decades threatens to choke out the quality existing among the best ones.

The foregoing was intended to demonstrate our comparative youth. We have grown so enormously in numbers that we have been unable to understand, or to meet our specialized ideological needs. We have burst our clothes. It would scarcely seem to be necessary to reiterate the facts of the fantastic growth of our specialty, except that there are so many in the top echelon who do not know, or knowing do not believe, or worse do not appreciate the significance of this growth. I do not know how much more the specialty can grow numerically. Certainly, the nation is not yet saturated with obstetric-gynecologic specialists. I do know that we have passed infancy and adolescence and stand on the threshold of maturity. Also, I know that unless we turn our attention away from mass production toward materially upgrading the quality of training throughout the nation, we cannot avoid invasion of our field by others who believe they know more about obstetrics and gynecology than we do.

Before attempting to assay the general level of our professional erudition, I would like to offer a few paragraphs concerning current customs, especially with regard to obstetrics. Correctly or not we elected to manage birth in the hospital rather than in the home, and by the doctor of medicine, be he generalist or specialist, rather than by the trained midwife. Why do we elect the hospital? For virtually all other physical functions except eating, we isolate ourselves. For the highly intimate family function of birth we bring the woman to the hospital, surround her with a group of strangers, and exclude her husband. In contrast, animals generally seek all possible secrecy at such



times. By transferring birth from the family into the hospital, we introduce considerable artificiality into our lives. I am sure this creates unspoken resentments and adds to criticisms leveled at us. We must explain that the only possible answer is increased safety. No other reason is tenable. Furthermore, North America represents the only large segment of the globe where obstetrics is managed almost exclusively by the doctor of medicine, usually a general practitioner. Obviously the specialist can handle only a small portion of the 4 million annual births in the United States. Probably command of maternal care by the doctor of medicine came about by chance rather than by election. With predictions that the number of births annually will increase by 2 million to a total of 6 million within a dozen years, it is obvious that the problem of supplying care on a mass basis, to say nothing of meeting informational and emotional needs of prospective mothers, will augment. There are some who advocate the training of nurse-midwives to act independently within the confines of the hospital, while remaining under medical supervision. This may be the answer to the challenge of supplying proper obstetric care on an ever-expanding front.

Pressing though the problem is, it is not shortage of quantity which interests me today. I am interested in the advancement of our specialty to the point where we are accorded our rightful place alongside our colleagues, to the point where people ask us, instead of tell us. Obviously this is intimately connected with, and inextricably bound to, the quality and caliber of our present practitioners, and to those of our residents in training. Earlier in the address, I postulated that we receive gratuitous advice from all sides because our specialty is young, and because our level of professional erudition generally leaves something to be desired. We have explored our youthfulness; allow me now to explore current levels of erudition. Attention, from this point on, will be concentrated on the specialist and those aspiring to be.

The obstetric-gynecologic specialist, as Dr. Morton pointed out, wangled his training in many devious ways. Only a few of the older men currently in practice were able to acquire acceptable bilateral residency training. The more recent the graduate, the better the chance that he was able to do so. Even so, there are many who never achieved either a broad medical or acceptable residency training. Others, for some time in practice, have allowed intellectual interests to relax in favor of patient volume. Unfortunately for the specialty as a whole, these are often the very individuals who bring down upon us the criticisms leveled at the group. The obstetrician who takes on an absurdly large number of patients, frenetically to keep busy, to satisfy his ego, to make money, or simply because his horizons do not encompass much more than the mechanics of birth, must inevitably slough something. Obviously office obstetrics including patient contacts and teaching are the first to be discarded. We all know such male-midwives who virtually live in the hospital and appear at the office, or home, infrequently. True, they work hard. I have known such men who delivered between 50 and 100 women each month throughout the year. Instead of sympathizing with the "dear, overworked doctor," I am appalled at the harm he does to obstetrics in general, through his failure to educate his



own community regarding good maternity care. In passing, I do not believe that any physician can give adequate maternity care to more than 200 women a year. Multiply 200 by 10 or 12 prenatal office visits, by the number of hours required to attend each woman in labor, and by the necessary puerperal care, and the truth of this statement becomes crystal clear.

The identical type is seen in gynecology whenever pride in technical skill supersedes all else. Again, each of us can call to mind a doctor who became technically brilliant in a certain type of operation, performing it repeatedly as a work-a-day routine. I might add that I knew one such who performed a hysterectomy on a 19-year-old girl, the girl's mother, and the girl's aunt, all in one morning. The surgical technician amasses large numerical series but, I would think, little else of value. One of the best technical surgeons I ever met never went to medical school and did not even have a college background! He was chief technician in a laboratory of dog surgery for 25 years.

The ordinary process of attrition will take care of men of this type in due course of time. What can we say about the young men coming forward to take their places? When the young doctor finishes his residency and his obligation to Uncle Sam, he is understandably anxious to see the dollars start rolling uphill toward him. On the other hand, he can hardly avoid making a good living today. We are told that our specialty is one of the most favorably compensated of all. With the market for young specialists in our field currently so favorable to them, I am afraid some of them become hypnotized by the dollar sign.

From my own personal experiences with a number of these young men, I sense an unfortunate tendency to learn certain treatments and techniques by rote, and to apply the knowledge with little discrimination. Most of you will recall the story of the little boy shuttling on errands back and forth between home and his aunt's house. After each errand his mother corrected him, and each time he slavishly applied the correction to the *next* errand. Unfortunately, and not infrequently, this story of the little boy, Epaminondas, can be appropriately told on Grand Rounds. Since cerebration is such a chore to all of us, we can scarcely blame young Dr. Kildare when he is so busy rushing around saving lives he doesn't have time to think. Dramatic action is so much easier than thinking, any day. Moreover, the residency setup, often supervised by different attending men unfamiliar with details of the patient's care, is not conducive to teaching habits of cerebration.

Regarding the average young obstetrician-gynecologist just starting practice, again permit me to draw upon personal experience. I have found that he either knows little, or is careless regarding such matters as: the scientific basis for the current emotion regarding radiation exposure, the genesis of certain congenital anomalies, methods of origin and mediation of pain from the pelvic organs, placental transmission, circulation of amniotic fluid, physiology of the newborn in general, and especially facts with regard to oxygen. The list could be expanded greatly, but is sufficient to sustain the basic premise. Clinically, he knows that if a laboring woman does not give birth vaginally

within a matter of hours, he will perform a section. He knows how to perform total hysterectomy and plastic vaginal repair, and little else. Generally, he has never done the minimum amount of intestinal surgery with which every good gynecologist should be familiar. The differential diagnosis of vesico- versus ureterovaginal fistula by simple means without the cystoscope, and the techniques of ureteral implantation are foreign to him. He may have heard of points "A" and "B," but knows little of radiation dosimetry and seldom has applied radium. Generally speaking, I am appalled by the almost total lack of intellectual curiosity of these young men. Have they not sufficient interest in the "why" and the "wherefore" occasionally to send them to the library? Before going further, I hasten to say that the indictment is directed at the residency and not primarily at the resident. He is the product of the system.

Some familiarity with the applications of the basic sciences to our speciality other than pathology, and with some of the less well-known clinical entities may represent useless information. Certainly such knowledge is not essential to the building of an enormous practice in America today. I believe the period of mass production of pseudo-specialists should end. It is time to stop flooding the country with poorly trained men whose sole excuse for recognition is that they will not hurt anybody. It is time to strengthen our training programs so that the number of such men decreases. It is my hope that, some glorious day in the future, successful completion of an obstetric-gynecologic residency will mean the introduction of one more truly competent specialist with potential to be a force for improvement in the profession and in his own community.

I do not believe that lengthening the period of residency training is the answer to the problem. At best such a course calls only a temporary halt to the assembly line. Moreover, it is frustrating to the good man to face a seemingly interminable training period. Must we, as teachers, keep good young men at subordinate levels for prolonged periods of time? Everything I know about training young men, and every instinct within me cries out "No" at such a policy. I think we can give the kind of men we would like to see in our specialty the necessary philosophies and technical training in a relatively few years. In other words, if the training is right, we can set his feet upon the path in a relatively short time. At this point some will ask how does one recognize good men? I am sure each of us within a few short months can differentiate between the man with and the one without the potentiality to learn the fundamentals of our specialty in a reasonable length of time. It is not necessary to eat all of an egg to know whether or not it is good or bad. We should improve the residencies we have and, above all, should turn our collective attention to quality production and ignore quantity. The obstetrician-gynecologist cannot handle, and currently does not handle more than a small part of the practical work of the specialty. The bulk of obstetric and gynecologic practice of America is handled by others, usually the general practitioner. Without a fantastic and totally unrealistic increase in facility and personnel, it will be forever impossible to alter this basic fact.

It seems to me that the quotation at the beginning of this address correctly defines the problem. Are we, as specialists in obstetrics and gynecology, ready, willing, and able to live up to our current billing as the focal point of maternity care, or, as I view it on a larger screen, the focal point of that segment of medical care devoted exclusively to woman? If we are, it will require unified effort on the part of many to insure orderly development under a democratic system, rather than under the guidance of one, two, three, or a dozen men, however dedicated they may be. It will require vision and a willingness to think and act cooperatively on a national scale. It must transcend the desire to preserve the status quo merely because of fear of change, or of consequences to established institution or dogma. The alternative is to concede that competent scientific knowledge of the female reproductive tract in health and in disease is too large a segment of medical knowledge for reasonably intelligent men to acquire.

Several years ago, I submitted a definition of the Specialty of Obstetrics and Gynecology to a group of my peers. They did not agree with it, and a subcommittee was appointed to revise the definition. After several intense hours, the subcommittee dissolved in disagreement.

In conclusion, I beg your indulgence to permit me to make another attempt along these lines, but this time to offer my idea of what a good specialist in Obstetrics and Gynecology ought to be:

First of all, he must be a good doctor of medicine. Second, he must be learned in those aspects of genetics, embryology, anatomy, physiology, pathology, and therapy, including surgery and irradiation, of the female reproductive apparatus and its anatomic surroundings, both in illness and in the physiologic exercise of the reproductive function. Finally, and equally as important as the other two, he must be thoroughly aware of the individual, of the psychobiologic integration of the woman possessing this apparatus. In short, he must be the WOMAN'S DOCTOR. Is this too much to ask of one man?



## HABITUAL ABORTION\*†

### A Report, in Two Parts, on 160 Patients

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**F**EW obstetric conditions have occasioned, among interested investigators, less consensus and more controversy than has the habitual abortion syndrome. Indeed, the number of theories of the causation appearing in the literature which purportedly explain the syndrome are, in point of disparity, only less remarkable than the number of therapies which are reportedly curative.

Despite multidirectional investigative efforts the problem of etiology has been approached, almost exclusively, along unidimensional lines. In the process, a variety of genetic, endocrinologic, anatomic, metabolic, and hematologic mechanisms have been described as being causally connected with habitual abortion. Thus, briefly and incompletely, defective germ plasm, hormone and vitamin insufficiency, incompetency of the cervix, incapacity and malposition of the uterus, chronic infection, and blood group incompatibility have all been specifically cited as antecedent mechanisml factors giving rise to recurrent spontaneous abortion.<sup>1-7</sup> Such a factorized etiological approach has, in its clinical application, led to a system of therapeutics which is notable for divergency rather than convergency.

Curiously, any of the many therapeutic regimens reported in the literature—whether in the prescriptive form of thyroid, progesterone, estrogen, relaxin, vitamin E, vitamin C, and vitamin K; or, in the proscriptive form of immobilization and sexual abstinence; or, in the inscriptive form of uterine suspensions and prophylactic purse-string procedures on the cervix—has been productive of results which, when compared with statistically derived spontaneous cure rates, range from good to excellent.<sup>8-13</sup> More curious is the fact that, while a given therapeutic regimen may, in the hands of one investigator, be conspicuously successful, the same regimen in the hands of another may, with comparable groups of patients, be just as conspicuously unsuccessful.

How are these theoretical and therapeutic inconsistencies to be explained? How, for example, can such fatalistic, and seemingly irreversible, theories of causation as repetitively defective germ plasm or recurrent blood group incompatibilities be reconciled with the high cure rates so variously obtained

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by so many workers? Similarly, if, as the literature suggests, there are multiple recurrent factors responsible for habitual abortion how can a single pharmacologic agent, say vitamin E or, more astonishingly, bismuth<sup>14</sup> be, for some, almost uniformly efficacious in unselected groups of habitual aborters?

The answers to such perplexing questions become all the more elusive when we consider the probability of spontaneous cure in habitual abortion. Authoritative statistical analyses indicate that spontaneous cure is significantly related to recurrent causal factors and that with each successive spontaneous abortion the likelihood of an underlying random or accidental causation decreases while the likelihood of a recurrent cause increases. Accordingly, with each successive spontaneous abortion the likelihood of spontaneous cure decreases exponentially. Thus, to use the figures of Malpas,<sup>15</sup> if a woman has had one previous miscarriage she has a 78 per cent chance of a spontaneous cure; with two previous consecutive abortions, she has a 62 per cent chance; with three, 27 per cent; and with four, only a 6 per cent chance of a spontaneous cure.

Since after three consecutive spontaneous abortions the chances are decidedly against spontaneous cure, and since most of the successfully treated habitual abortion groups reported upon consisted of women with histories of three consecutive miscarriages, the element of fortuity seems to be highly unlikely. By the same statistical token, it appears that, multiplicity and diversity of approach notwithstanding, any therapeutic regimen which was successful upon significant numbers of patients was somehow curative.

This brings us to a consideration of the nature of the curative process in habitual abortion. While our knowledge in this regard is limited, meaningful inferences and working hypotheses can be made from presently known facts. Of more than speculative interest in this regard are the almost cyclical clinical trends which occur with the introduction and enthusiastic advocacy of new "therapies" for habitual abortion. Usually, and, to some extent, in proportion to the professional stature and persuasiveness of the advocate, each new and therapeutically dramatic regimen is eagerly seized upon by corroborating fellow enthusiasts. In time, with more extensive and less suggestible usage, disenchantment usually sets in and, in the process, the drug loses its efficacy. Our manic-depressive experience with relaxin is a recent case in point and adds substance to Trudeau's nineteenth century admonition to young physicians: "Make haste to use the new drugs while they are still effective."

#### Part I. The Role of Emotional Determinants

In the light of the foregoing the question arises as to the possibility of the curative process hinging not upon any "proved" specific curative agent but, instead, upon some extraspecific factor present in all of the cited therapies. Such a common factor might have to do with the therapist's personality and, in turn, with the witting or unwitting psychotherapeutic use made of it in relation to abortion-prone women.

*Previous Psychophysiologic Approaches.*—Since, in recent years, various functional pathways from the cerebral cortex through the higher autonomic

centers and pituitary-adrenal axis have been described<sup>16, 17, 18</sup> by way of which psychogenic sterility and abortion may occur, such a hypothesis is physiologically plausible. Indeed, the work of Alvarez and Caldeyro-Barcia<sup>19</sup> clearly demonstrates, by way of electromanometric recordings from balloons buried in the myometrium of a large series of pregnant women, that intense uterine contractions can occur in response to certain types of experimentally induced emotionally painful situations. Similarly, uterine irritability and ischemia in the face of emotional stress have been described.<sup>20</sup> Added to this are the clinical observations of both obstetricians and psychiatrists<sup>13, 21, 22</sup> who have noted a seeming relationship between emotional factors and habitual abortion.

*Methods of Present Investigation.*—Despite such provocative observations very little validating information from a psychodynamic standpoint has been forthcoming. In the virtual absence of previous psychiatric studies upon significant numbers of these patients, a special clinic was established in 1954 for habitual aborters seen at the New York Lying-In Hospital.<sup>23, 24, 25</sup> This clinic is limited to those abortion-prone women who present a history of at least three consecutive spontaneous abortions. The abortions may have occurred either in the absence or presence of previous parity. In the former event the individual is termed a primary habitual aborter, and in the latter, a secondary habitual aborter.

Each patient upon admission to the clinic undergoes a thorough gynecologic work-up which includes hystero-graphy and intrauterine balloon studies. In the absence of discernible abortigenic pelvic abnormality the patient is then seen in a series of preconceptional psychiatric interviews.

While the interviews are geared to uncover basic psychodynamic information, their equally important function, from a therapeutic standpoint, is to acquaint the patient with the possibilities of an emotional approach to her abortive disabilities and of then gaining her confidence in this approach. Although the method utilizes uncovering techniques and, to a limited extent, "insight," it is for the most part an experiment in relationship therapy. For reasons to be discussed later these patients usually invest heavily, from an emotional standpoint, in the relationship and usually are able to turn this investment to profitable account in terms of increased self-acceptance or self-assurance. In the process they develop confidence in the relationship. From confidence in the relationship to confidence in its therapeutic possibilities is an easy step for most of these patients who, as the literature seems to attest, respond favorably to any approach which has their trust.

*Results of Therapy.*—During the first three and one-half years of this exploratory study 160 habitual aborters were seen, gynecologically evaluated, and followed. Of this number, 2 were found on hystero-gram to have bicornuate uteri for which unification procedures were performed. An additional 13 were found, by way of newly devised intrauterine balloon studies, to have an "incompetent internal cervical os" and either have had or are going to have corrective surgery.

The remaining 145 were found to be free of gynecologically discernible abortigenic conditions and comprise the study as it relates to the psychosomatic method of therapy previously outlined. Of this number, 57 have been delivered of normal living infants, 13 have miscarried, 21 are in various stages of pregnancy, 6 have dropped out of treatment before becoming pregnant, and 48 are still in the preconceptional phase of therapy. Considering only the patients in the study group who, by virtue of delivery or abortion, responded successfully or unsuccessfully to psychotherapy, we have a total of 70 patients. While from a statistical standpoint this number is small, comparison of outcome of pregnancy before and after such treatment merits

mention. This group, among whom were 19 secondary aborters and 51 primary aborters, had, prior to treatment, a total of 290 pregnancies, 265 of which ended in miscarriages and 25 of which ended in viable births. Expressed comparatively, 91 per cent of all pregnancies before treatment ended in abortion; with treatment, 19 per cent ended in abortion.

*Psychological Description of Study Group.*—Viewed in a psychological perspective these patients have been found to be remarkably alike in many emotional respects. Perhaps the most striking similarity is to be found in their tendency to react somatically to psychic situations. This tendency is most marked in the more immature and dependent habitual aborters who usually present lifelong histories of psychosomatic reactivity which they themselves associate with certain types of emotionally stressful situations. Such patients, who in number approximate one half of the study group, are inveterate visceral reactors who as children developed nausea and vomiting in the face of a quarrel between the parents, or who upon becoming engaged to their husbands developed colitis, or who after losing a tiff with a redoubtable mother-in-law developed a headache. In some instances these patients are painfully self-conscious of their psychosomatic propensities and, in consequence, they almost phobically avoid those emotional situations which are most apt to evoke a psychosomatic response. More frequently, they come to regard their disabilities in this connection as a condition to life and, in the words of one such patient, deplore but accept the fact that they lack "built-in" tranquilizers.

Of seeming predisposing significance is the almost uniform type of family background reported by such patients. As a rule the patient was brought up in a home in which the mother was the dominant, constant, and dependable parental figure. More importantly, the mothers are described as being compulsively overprotective in such a way as to cause the patient to become more or less addicted to a dependent style of life which she fails to outgrow. Her failure in this latter regard is usually potentiated by the father, who is less remarkable for what he did than for what he did not do. That is to say, instead of being available to lessen the patient's dependent investment in her mother by increasing her investment in him, he is usually lost to the patient early in her life either through death, desertion, or divorce, or, more frequently, through alcoholism, self-distance, or passive ineffectualness which renders him an object of weakness or contempt in the eyes of the mother and, through identification, the patient.

In the presence of an overly possessive and protective mother who virtually insists upon dependent compliance and in the absence of intercessive action on the part of the father, the child is typically delayed in her psychosexual development. Throughout her adolescence she continues to be raised as more a child than a daughter and, after marriage, tends to dramatize her marital partner as less a husband than a mother substitute. Although able to perform her domestic duties adequately she tends to regard herself as lacking in womanly status and to equate femininity, particularly as it relates to motherhood, with an idealized maturity which transcends her adaptive ability. Not feeling yet quite like a woman she finds it uncomfortable to perform like one. It is in the performance of the most basic womanly function, procreation, that this conflict becomes most apparent.

Perhaps nowhere else is this conflict more apparent than in the transparent dream life reported by these patients. Many, for example, are recurrently subject to dreams in which they successfully carry a pregnancy to term only to find at the end of the dream that the infant is a doll rather than a baby. Similarly, they frequently have dreams in which they are



figured as being children again and being pregnant. Two such patients varied this theme slightly by repeatedly dreaming that Shirley Temple was about to give birth.

This preconscious tendency to associate their childlessness with childishness seems to stem from an anticipatory type of fearful self-doubt. Of interest in this connection is the frequency with which "performance phobias" are elicited. Not uncommonly these patients recall episodes of somatized panic in response to situations in which they were, in one way or another, called upon to perform. The type of the performance and response vary according to the context in which they occur and have ranged from loss of voice while being featured at a recital to the development of severe and uncontrollable diarrhea during the course of a college entrance examination.

It seems, with many of these patients, that whenever they are under emotional pressure to carry out certain types of activity successfully, anxiety is mobilized and translated somatically into some action which precludes success, although successful completion of the activity would ordinarily be well within the range of their ability if performed automatically with no pressure and no emphasis upon performing successfully. Their responses in this regard represent a kind of intention tremulousness which may involve virtually every organ system, including the reproductive.

Indeed, this tendency, for reasons previously discussed, becomes most pronounced in pregnancy, when in response to fearfulness and regression they tend to develop uterine contractions which may lead to decidual hemorrhage and miscarriage. Treatment, consequently, is directed at converting the patient's maternal desires into expectations and, then, at maintaining her motivation toward motherhood at a sufficiently high level to withstand regressive tendencies.

While approximately one half of the study group present histories of psychosomatic reactivity occurring under a variety of emotionally disturbing circumstances, there are others who react psychosomatically only to very specific types of emotional conflict.

This type of reaction has proved to be most striking in the patients who present histories of a premarital pregnancy and criminal abortion. This subgroup of habitual aborters, quite surprisingly, makes up approximately one third of the study group. Being unable to demonstrate, by way of hysterographic contour studies, the presence of cervical or uterine damage, we proceeded, early in our work, on the assumption that unresolved guilt associated with the criminal abortion represented a continuing unconscious conflict which, in somatic translation, resulted in expiatory spontaneous abortions. This assumption, which we began to test by way of abreactive psychotherapy, gained even more convincing status with the remarkable histories being obtained.

Of significance in this regard was the frequently glaring psychodynamic meaningfulness of the symptomatic context in which the abortions recurred. One patient, for example, recurrently miscarried on Mother's Day and another repetitively aborted on the anniversary date of the criminal abortion. Despite such symptomatic transparency, which was frequently in evidence, practically all of these patients resisted awareness of the possible relatedness between the criminal abortion and their more current abortive disabilities. One anniversary aborter, for example, after spontaneously aborting on the anniversary date of her criminal abortion on two occasions, became convinced of a causation other than coincidental and, in her naïveté, attempted to circumvent destiny by becoming pregnant nine months prior to the anniversary date which would then be her expected date of confinement. Even when this contrived pregnancy ended in an early spontaneous abortion and she despaired



of a self-cure it was not until after several months of psychotherapy that she was able to accept, less tangentially, the guilty connection and enter into another pregnancy.

Such patients, despite their initial resistance to confrontation with and acceptance of unresolved feelings of guilt, respond very favorably to a psychotherapeutic approach. Our results with this subgroup of habitual aborters, in respect to successful pregnancies, has been approximately 85 per cent.

*Comment.*—By way of summary, suffice it to say that, in the course of this exploratory psychiatric investigation of habitual abortion, definite psychologic patterns have emerged which point to a relationship between emotional factors and the abortion habit. While some light has been shed upon the nature of these emotional factors and of their modifiability, much work remains to be done in bridging the gap between emotional causation and physiologic effect. Since many of the mechanisms described as being causally connected with habitual abortion may represent distant links in the causal chain and since the more central links may arise out of neurohumeral disturbances associated with emotional determinants, future research should aim at the vitalistic and multilevular as well as at the peripheral and unilevular.

## **Part II. Anatomic Determinants and a New Roentgenologic Method for the Diagnosis of Cervical Incompetency**

As was indicated in Part I, each of the 160 habitual aborters comprising the series was thoroughly investigated from a gynecologic standpoint. A hysteroqram was performed on each patient and in the presence of abnormal hysteroqratic findings a dilatation and curettage was done. This latter procedure proved to be remarkable only in a negative sense; that is to say, except in the 2 instances of bicornuate uteri, the abnormal intracavitary findings on hysteroqratic were not confirmed on curettage or, at a later date, when postabortally or postpartally the uterus was manually explored. Similarly, retroversion of the uterus and subserous myomas appeared to play little, if any, causative role in habitual abortion. The incidence of subserous myomas in both our successes and failures was approximately 10 per cent. The incidence of retroversion in our successfully delivered patients was 18 per cent and in our failures less than 10 per cent.

*Cervical Incompetency.*—Just as conventional hysteroqratic proved to be, for the most part, an ambiguous evaluative tool, the existing radiographic methods for determining cervical incompetency were also found to be unreliable. This was all the more regrettable in view of observations, emerging early in the study, which pointed to cervical incompetency as a definite and not infrequent clinical phenomenon associated with habitual abortion.

These observations were related to the striking regularity of clinical events which presaged and seemed to be a condition for a particular type of abortion. This type of abortion, which typically occurred from the sixteenth to the twenty-eighth week of gestation, was most remarkable in that the cervix, in the absence of perceptible uterine contractions or uterine irritability, underwent premature effacement and loss of tonus. This painless and apparently passive process was observed to take as long as a week for complete effacement during which time there was a clear, colorless, watery vaginal discharge and progressive softening and loss of cervical substance. Coincidentally with completion of effacement there was a loss of cervical sphincteric action with resultant prolapse of the intact membranes and dilatation of the cervix. Uterine contractions would then secondarily supervene and abortion would become inevitable.

How and why these cervical changes occur are but poorly understood. To begin with, the dynamic means by way of which the cervix maintains its sphincteric function during pregnancy remains controversial. Much of the controversy is related to investigative disagreement as to the fate of the isthmus during pregnancy. The isthmus was originally described in the non-pregnant uterus by Aschoff<sup>26</sup> as consisting of an area of transition between the cervix and corpus and as being bounded by superior and inferior ora. The lower os, which he termed histologic internal os, marked the point of transition from typical cervical mucosa to the mucosa of the isthmus, which, while resembling the mucosa of the corpus, was thinner and contained fewer glands. The upper os, termed anatomic internal os, marked the point where the narrow upper part of the cervical canal broadened out to form the cavity of the uterus.

Until recently most investigators,<sup>26-29</sup> on the basis of anatomic specimens of pregnant uteri, were unable to demonstrate the presence of an upper internal os after certain stages of pregnancy and, in consequence, assumed that an "unfolding" of the isthmus occurred during pregnancy. The time at which this unfolding was said to occur varied with the investigator; however, the consensus was that in the first or early second trimester of normal pregnancy unfolding of the isthmus segment occurred and that, in the process, the so-called internal os (i.e., the anatomic internal os of Aschoff) lost its identity, as did the remainder of the isthmus canal, which was incorporated into the uterine cavity, becoming a part of it.

More recent investigations<sup>30, 31</sup> indicate that the unfolding of the isthmus observed by earlier workers may well represent an *in vitro* rather than an *in vivo* finding. Indeed, Asplund,<sup>31</sup> by way of hystero-graphy performed upon 26 pregnant women, was able to demonstrate unequivocally the presence of the intact isthmus as late in pregnancy as the sixth month. His hystero-graphs of pregnant uteri disclosed an isthmus which, in many cases, did not differ appreciably from that of the nonpregnant uterus and, more constantly, an isthmus which, in contradistinction to any unfolding tendency, was longer and narrower than the nonpregnant isthmus.

In the light of Asplund's compellingly objective research it appears that, during pregnancy, the isthmus is a distinct and continuing entity; that its role is probably sphincteric; that this sphincteric role is functionally rather than anatomically determined; and that unfolding of the isthmus as observed by earlier investigators quite possibly represents an anatomic artifact occasioned by relaxation of the isthmus following surgical removal of the uterus. That functional relaxation can occur in the nonpregnant state is shown by the work of Liesse,<sup>32</sup> who has demonstrated a decrease in isthmus tone following the infiltration of the uterosacral ligaments with a local anesthetic.

Viewed in this perspective the isthmus is operationally, as well as histologically, transitional, serving a cervical function throughout most of pregnancy and a uterine function only during the terminal phase of pregnancy when, perhaps as a condition of effacement of the cervix, unfolding occurs. Accordingly, cervical competency would, in large measure, depend upon the integrity of the isthmus. In support of such a view is the work of Palmer,<sup>33</sup> who in 1950 reported upon hystero-graphy in 44 cases of habitual abortion. He found that the isthmus was abnormally wide in 5 of 6 cases in secondary abortion, and in 5 of 36 cases of primary abortion. Earlier he and Lacomme<sup>34</sup> had reported upon a "gaping" internal os as a possible cause of habitual abortion. Similarly, Shirodkar<sup>35</sup> in India, and Lash and Lash<sup>4</sup> in this country have reported upon cervical incompetency as a cause of habitual abortion and upon pre- and postconceptional corrective surgical procedures.

*Unreliability of Present Diagnostic Methods.*—Unfortunately, the methods in use by which cervical incompetency is diagnosed remain more impressionistic than scientific. Hystero-graphy which utilizes a withdrawal film, taken immediately after the removal of the cannula from the dye-filled uterus, has been the diagnostic method most commonly used to outline the cervix and its upper reaches. In practice, withdrawal films have proved to be unreliable on several counts. To begin with, the cervix and isthmus, more often than not, are indistinctly or incompletely outlined, making interpretation difficult if not impossible. Even when the films are of good "diagnostic" quality the degree of dilatation of the isthmus, in the absence of known pressure gradients and comparison standards, is so relative as to be unquantifiable. As a result, this method, at best, is suggestive rather than diagnostic and, at worst, may mislead the observer into false positive and false negative conclusions.

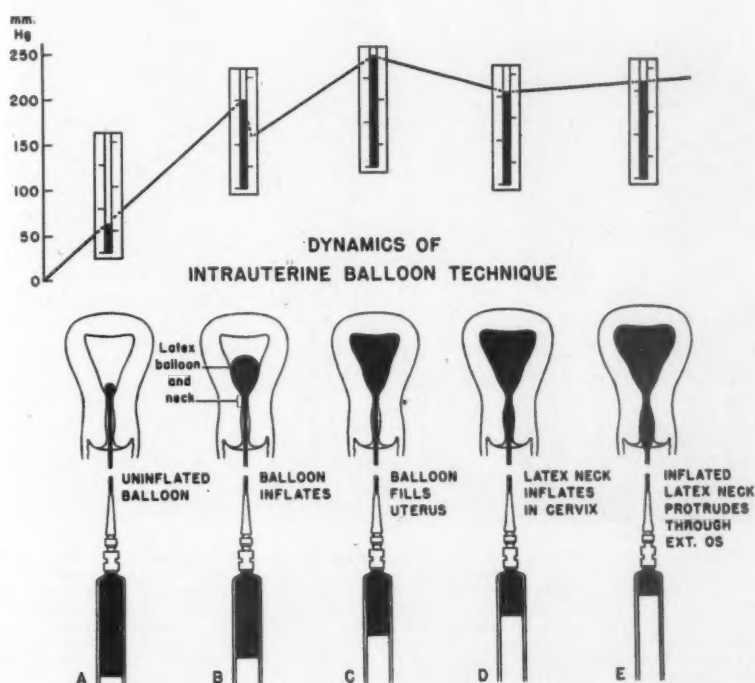


Fig. 1.—A stepwise representation of the dynamics involved in the intrauterine balloon technique. In A, the balloon is in the process of being inflated with radiopaque material. Initially, and before the balloon begins to inflate, the pressure within the balloon must rise to approximately 200 mm. Hg, at which point inflation occurs. Coincidentally with inflation there is a sharp drop in pressure within the balloon (B). With continuation of the injection the balloon continues to increase in volume until it fills the endometrial cavity. As the balloon fills the cavity and adapts to its contours there is a progressive increase in pressure. A second critical point in pressure (C) is reached when the enlarging balloon encounters myometrial resistance sufficient to cause the latex neck of the balloon to inflate below the level of the anatomic internal os. Again there is a drop in pressure (D). Further injection results in expansion of the latex neck within the isthmus and upper cervix. With increased intraisthmic and endocervical resistance, expansion progresses downward, culminating in protrusion of the latex neck through the external os (E).

Because of the defects inherent in the "withdrawal" techniques, an alternative and supplemental method was introduced in 1953 by Lash and co-workers.<sup>36</sup> This method entails the use of varisized balloons attached to the tip of a metal cannula. Depending upon the estimated size of the uterine cavity a smaller or larger balloon is introduced into the uterus. Aqueous dye is then, by way of a syringe attached to the metal catheter, forced into the



intrauterine balloon. After the balloon is filled and has assumed the shape of the uterus, a film is taken. Downward traction is then exerted on the metal cannula and, as small amounts of dye are successively withdrawn, the balloon is pulled through the isthmus and cervix during the course of which serial x-rays are taken.

While this method is diagnostic in cases of marked cervical incompetency it is, again, useful only as a gross type of clinical indicator and, involving as it does such unmeasured variables as traction and pressure, has little research value as a test instrument by which less-pronounced cervical incompetency can be accurately defined.

In the absence of a more definitive test for cervical incompetency an increasing number of obstetricians and gynecologists<sup>37, 38</sup> are now making the diagnosis and operating on the basis of history alone. In the process, an increasing number of patients are being subjected to operation on the historical

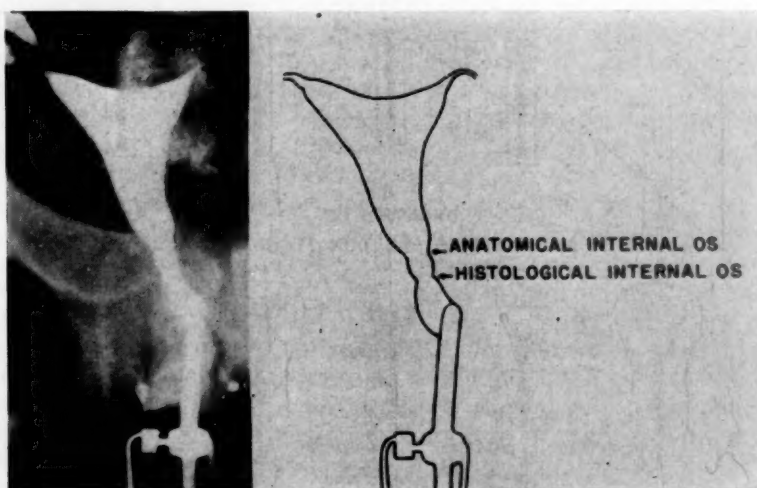


Fig. 2.—Normal isthmal landmarks as revealed by hystero-graphy. Fig. 2 is included as a frame of reference for the illustrations which follow. As will be recalled the isthmus is bounded by the anatomic internal os, superiorly, and by the histologic internal os, inferiorly. Asplund's hystero-graphs taken as late in pregnancy as the sixth month graphically reveal that the isthmus, during pregnancy, does not differ appreciably in appearance from the non-pregnant isthmus and that variations, when they occur, reveal an isthmus which is longer and narrower than the nonpregnant isthmus. His findings indicate that the isthmus serves a cervical and sphincteric function until the terminal phases of pregnancy when unfolding of the isthmus into the lower uterine segment occurs.

basis of recurrent middle trimester miscarriages. In our experience such a criterion would appear to be of dubious validity inasmuch as 20 per cent of the patients in our series who were successfully treated by psychosomatic methods had theretofore recurrently aborted in the second trimester.

*Experimentation With and Refinement of a New Diagnostic Method.*—With the need in mind for a test instrument by way of which cervical incompetency could be accurately defined, we began early in the study to experiment with various types of intrauterine balloons. In the interest of standardization these studies were always performed during the proliferative phase of the menstrual cycle. Early in our experimentation it became apparent that any intrauterine balloon which expanded in one stage would herniate down into the isthmus only when the isthmus was markedly hypotonic and, even then, only under extreme pressure. Consequently, we began devising balloons which expanded in two stages. To accomplish this we developed an expansile



unit consisting of a small latex balloon to which was joined a latex neck. This expansile unit was, in turn, joined to a hard rubber catheter the open end of which was utilized for the injection of aqueous radiopaque dye. Introduction of the upper portion of the expansile unit into the uterus and of its lower portion into the isthmus was effected by way of a stylet. With the introduction of dye the intrauterine portion of the expansile unit expanded, adapting to the intrauterine contour. With increasing myometrial resistance there was a concomitant rise in pressure within the balloon. After a critical

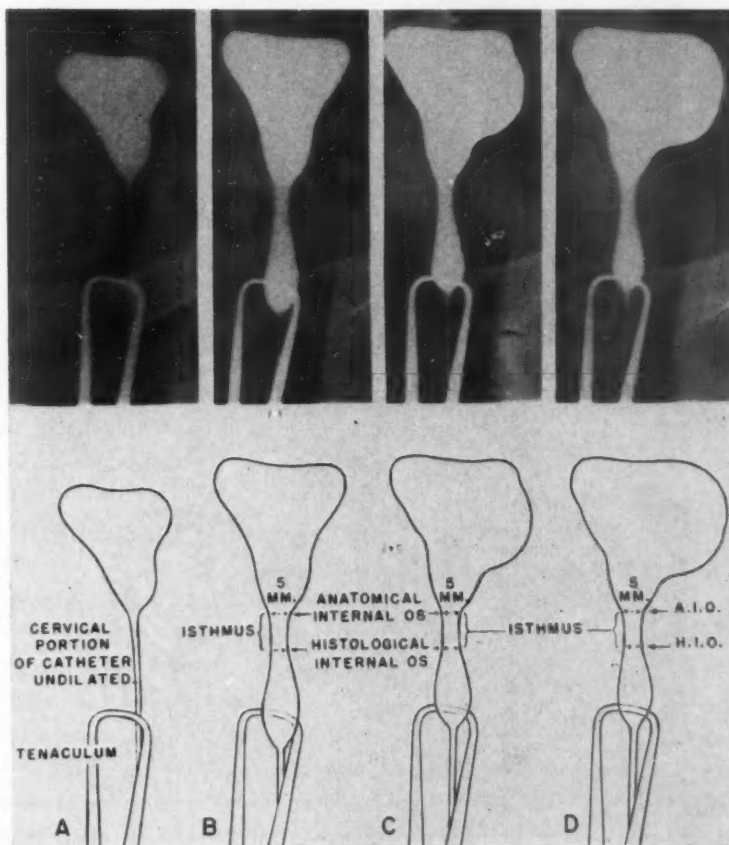


Fig. 3.—Illustrates, by way of film and film tracings, cervical competency as revealed by the newly devised intrauterine balloon technique. Film and film tracing (A) reveal the balloon to fill the uterus. It is at this point during the test that the patient will perceive sudden but mild uterine discomfort. With an increased amount of dye being injected, myometrial resistance raises the pressure within the balloon to a critical level (approximately 250 mm. Hg) at which point the neck of the balloon, lying in the upper reaches of the isthmus and cervix, expands (B). With the introduction of additional dye there is increased pressure, evidenced manometrically and, in this particular illustration, by adaptive regional hypotonia of the fundus (C). Despite increased pressure the isthmus, particularly the anatomical internal os, does not dilate, as do the fundus and lower cervix. Instead the width of the isthmus remains narrow and constant, revealing cervical competency.

pressure had been reached the intraisthmic portion of the expansile unit would then secondarily expand below the level of the anatomical internal os and, in the process, outline the isthmus and entire endocervical canal. In this way, not only was delineation of the isthmus and cervix possible, but changes in endocervical and intra-isthmic caliber, under controlled pressures, were obtainable.

Since the capacity of the balloon depended upon the length of its adjoining neck and since in very large and hypotonic uteri the neck of the balloon was incorporated into the expanding balloon before myometrial resistance was encountered, it became necessary to vary the length of the balloon neck according to the size of the uterus. Accordingly, the balloons currently being used have expansile capacities of from 20 to 30 c.c. depending

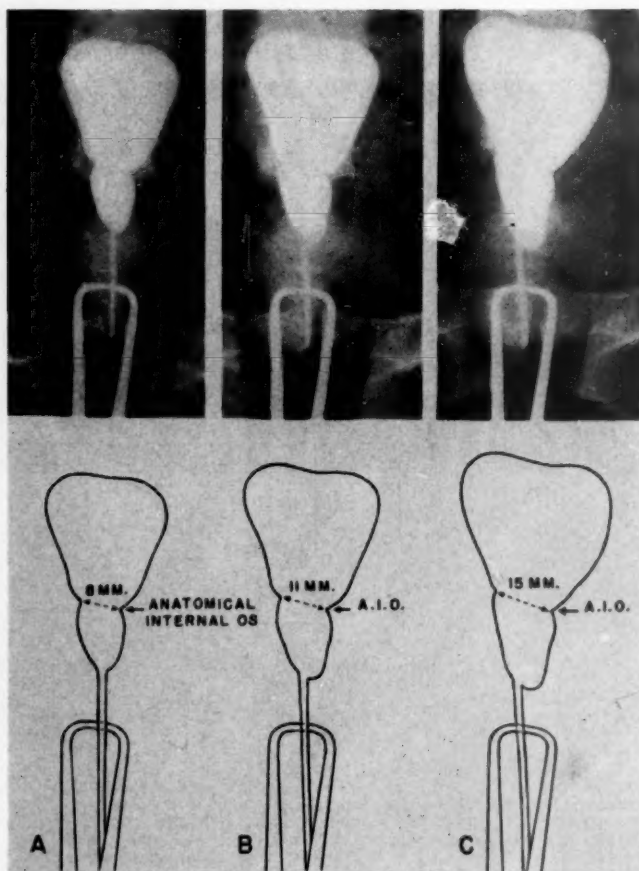


Fig. 4.—Illustrates, again by way of film and film tracings, cervical incompetency. Film and film tracing A reveal expansion of the balloon within the uterus and expansion of the neck of the balloon within the isthmus and upper cervix. The lower boundary of the isthmus, as is frequently the case in cervical incompetency, has lost its functional identity and only the anatomic internal os definitely remains. With increasing amounts of dye and concomitant increases in pressure the anatomic internal os progressively and abnormally widens (B and C), revealing cervical incompetency.

The patient upon whom these films were taken became pregnant after the diagnosis of cervical incompetency was made. She was followed closely on a weekly basis and in the twentieth week of gestation developed a premature cervical effacement which over a period of a few hours culminated in herniation of the membranes through the effaced cervix which dilated passively to 3 cm. At this point, in the absence of uterine contractions, a purse-string closure of the cervix was performed. Fourteen weeks later, after an uneventful postoperative course, she went into labor. The purse-string suture was cut and she was delivered of a 2,000 gram infant who has since done well.

upon their length. A process of equilibrating, on a one-to-one basis, the number of centimeters to which the uterus sounds with the length in millimeters of the balloon neck is now in progress and, thus far, has proved to be satisfactory.

*Comment and Direction for Future Research.*—While the intrauterine balloon just described appears to be definitive in its diagnostic potential, it was

only recently, after many revisions, that it became a precise research instrument. In consequence, much work remains to be done with both control and habitual abortion groups before the borderline zone between cervical competency and incompetency can be accurately defined. Added to the problem of accurate definition is the complicating possibility of a functional type of cervical incompetency which is reversible and which, appearing only during pregnancy, is undiagnosable in the nonpregnant state.

Our work thus far indicates that marked isthmie hypotonia, as demonstrated under the experimental conditions previously outlined, correlates closely with impaired sphincteric function of the cervix during pregnancy. Indeed, in its extreme form it is reproductively crippling. Of the 13 patients in our series who were found to have unequivocal evidence of incompetency, 10, for investigative reasons, were not offered preconceptional surgery but instead were followed through a pregnancy after the diagnosis had been made. Of these 10 patients 8 had remarkably similar gestational courses characterized by passive dilatation of the cervix with herniation of the membranes through the external os at periods of gestation which ranged from the sixteenth to the twenty-eighth week. The other 2 patients, contrary to the maxims of the literature, aborted in the first trimester. In both instances the abortions occurred in the eighth week of pregnancy and were unusual in that both occurred without premonitory warning, each being characterized by precipitate, painless, and complete expulsion of the products of conception. Thus, in our experience, an incompetent internal cervical os or, more accurately, a markedly hypotonic isthmus, diagnosed in the nonpregnant state is, in the absence of pre- or postconceptional surgery, an irreversible condition which precludes a successful pregnancy.

With a definitive test instrument at our disposal we now plan to study systematically uterine, isthmal, and cervical dilatation and tonus under controlled volumetric and manometric conditions. In this way we hope not only to define cervical incompetency more accurately but, in the process, to learn more about the physiology of the isthmus and cervix. Indeed, many unproved observations such as increase in width of the isthmus during the proliferative phase of the cycle, or the narrowing of the width at ovulation, or spasm of the isthmus as a frequent cause of sterility can, with this instrument, be quite accurately validated.

I am indebted to Dr. Elaine Grimm who, as clinical psychologist for the project, psychometrically evaluated the study group; to Dr. William McLarn whose collaboration was indispensable in the radiographic studies, and, finally, to Dr. R. Gordon Douglas who, in countless ways, made the study possible.

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## FETAL MORTALITY AND PREMATUREITY WITH REPEAT ABDOMINAL DELIVERY\*

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IT HAS been shown that fetal mortality is greater with cesarean section than with vaginal delivery.<sup>1-2, 6, 8, 10-12</sup> The greater loss is generally attributed to the obstetric complication leading to the hysterotomy and not to the operative procedure. Fetal salvage, even with repeat cesarean section, may, however, be less favorable than with the average delivery, for babies born under this circumstance are not infrequently premature.

This study concerns the higher fetal mortality with repeat abdominal delivery, its relation to prematurity, and measures that may be used to improve the situation.

### Material

Nine hundred and thirty-four repeat abdominal deliveries were collected from 6 of 7 hospitals serving the Knoxville area, defined as including Knoxville, Maryville, and Oak Ridge, Tennessee. Table I gives the total incidence of cesarean section, the number of primary and repeat abdominal deliveries, the total number of births, and the period of study for each hospital. The survey covers a 10 year period. There are exceptions in the cases of hospitals No. II and VI that were opened in 1947 and 1956, respectively. Some of the other hospitals were opened or closed during the period of study. Most of these had an open staff.

TABLE I. PERIOD OF STUDY, NUMBER OF BIRTHS, NUMBER OF CESAREAN SECTIONS, AND INCIDENCE OF CESAREAN SECTION FOR EACH HOSPITAL

HOSPITAL	PERIOD OF STUDY	TOTAL BIRTHS	CESAREAN SECTIONS		
			PRIMARY	REPEAT AND UTERINE RUPTURE	TOTAL INCIDENCE (%)
I	1/1/48 to 1/1/58	9,853	93	84	1.8
II	8/1/47 to 1/1/58	13,356	517	217	5.5
III	11/15/48 to 1/1/58	16,138	286	207	3.0
IV	1/1/48 to 1/1/58	15,449	355	353	4.6
V	1/1/48 to 8/1/56	11,239	169	59	2.0
VI	8/1/56 to 1/1/58	1,408	22	14	2.5
Total		67,443	1,442	934	3.5

Fetal mortality includes all stillbirths and neonatal deaths of infants of 20 weeks' gestation or more up to the time the infant was discharged from the

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hospital. Most normal babies went home within the first 7 days of life. Premature infants otherwise normal usually were hospitalized until they weighed 2,500 grams or more. A premature baby is defined as one weighing 2,500 grams or less or under 36 weeks' gestation.

The annual combined stillbirth and neonatal death rate for all deliveries was obtained by taking the average for Anderson, Blount, and Knox counties wherein the Knoxville area is located. This figure was unavailable for the year 1957. The neonatal period was the first 28 days of life.

The majority of indigent patients were housed in hospitals V and VI while private patients comprised most of the admissions to the others.

Before 1953 most cesarean sections were of the classical type and usually performed under inhalation anesthesia. After 1952 the low-segment operation predominated and regional anesthesia was used more commonly.

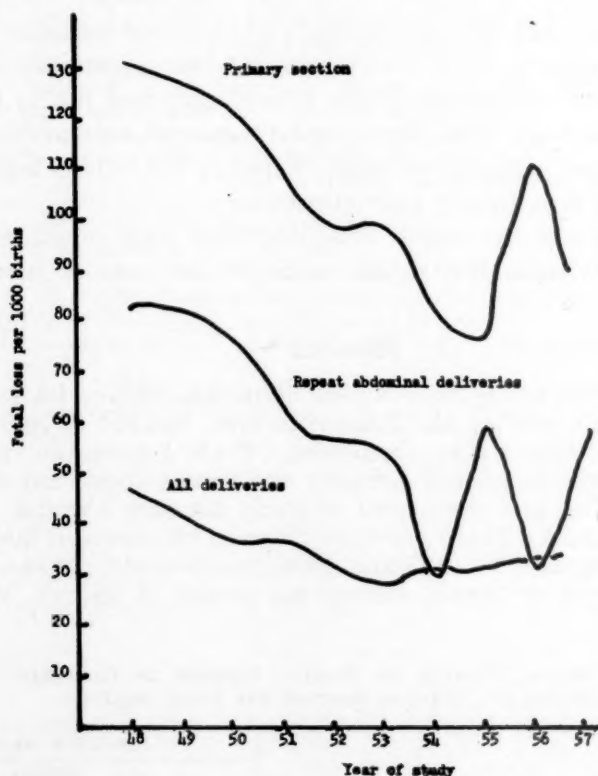


Fig. 1.—Fetal mortality by year for primary section, repeat abdominal deliveries, and all deliveries.

### Results

**Fetal Loss.**—There were 928 single births and 6 sets of twins born by repeat cesarean section or following rupture of the uterus. Sixty-one babies (20 stillbirths and 41 neonatal deaths) were lost and 879 discharged alive. The over-all mortality rate was 6.5 per cent. Thirty-six of these babies, or 7.8 per cent, were lost in the first half, as compared to 25, or 5.2 per cent, lost in the last half of the study period. The over-all loss of 6.5 per cent is to be contrasted with 3.5 per cent for all deliveries and 10.7 for primary cesarean section. A breakdown of each category by year is shown in Fig. 1. Because of great differences in the number of patients within each category, only trends can be shown. The



drops in mortality rates with abdominal deliveries in 1951 and 1954 followed extensive maternal and fetal mortality studies and more active mortality conferences in the various hospitals.<sup>6</sup>

*Rupture of the Uterus.*—One reason that fewer babies were lost in the last 5 years than in the first 5 years of the study was that rupture of the uterus with loss of the infant was less common (Table II). Presumably better operative techniques were beneficial in this respect. All ruptures were subsequent to the classical operation.

TABLE II. RUPTURE OF THE UTERUS IN 21 PATIENTS\*

	1948-1953	1953-1958
No. of repeat sections	444	474
No. of babies born following rupture of the uterus	18	4
Ratio of ruptures to total repeat sections	1:25	1:119
No. of babies lost	14	3
No. of babies saved	4	1

\*Twenty-two babies born.

Seventeen of the babies born under this circumstance were stillborn; the other 5 survived. One mother died as a result of a uterine rupture. Some others required heroic treatment.

Seven of the 22 babies were premature, 3 weighed 1,500 grams or less. The remaining 15 babies ranged in weight from 2,750 to 5,200 grams.

*Weight of Babies.*—Fetal loss is correlated with the weight of the baby in Table III. One half of the infants who died were premature. Thirty-one of the 101 premature babies died. Thirteen of these died as a result of some obstetric complication or fetal anomaly. The other deaths were after elective delivery. The incidence of prematurity was approximately the same for the two 5 year periods of the study. Most of the babies weighing less than 2,000 grams were delivered between 1948 and 1953. All but 5 prematures who died between 1953 and 1958 were associated with some maternal complication (Table IV). None of the premature babies born in hospital No. I were delivered by elective repeat cesarean section. Under similar circumstances only 2 of more than 100 infants delivered in hospital No. II in the last 5 years of the study were premature. These 2 infants weighed 2,250 grams or more.

TABLE III. WEIGHT OF BABY AND MORTALITY RATE

WEIGHT (GM.)	NO. OF BABIES	BABIES LOST	
		NO.	%
Over 4,000	60	1	1.6
2,500 to 4,000	757	26	3.4
2,000 to 2,500	82	20	25.0
1,500 to 2,000	15	7	46.6
Less than 1,500	4	4	100.0
Unknown	22	3	14.0
Total	940	61	6.5

TABLE IV. INDICATION FOR REPEAT ABDOMINAL DELIVERY AND FETAL MORTALITY

INDICATION	NO. BABIES	NO. BABIES LOST
Elective	863	40*
Maternal complication or premature labor	77	21
Total	940	61

\*Eighteen babies premature. Thirteen of these died in first 5 years and 5 in last 5 years of the study.

*Indications for and Timing of Cesarean Section.*—The majority of repeat cesarean sections were done electively 7 to 14 days before the expected date of delivery as calculated by Naegele's rule (Table IV). Forty babies born under this circumstance were premature. Eighteen of these died.

Five of the 12 twin babies died but none after elective operative intervention.

Physicians variously used radiographic studies of the fetus in utero and evaluation of the ripeness of the cervix and mensuration of the crown-rump length of the fetus determined by palpation to substantiate that the pregnancy was at term before a cesarean section was done. None of the babies delivered electively was premature, except an occasional one with an anomaly, if it was determined beforehand that the epiphyseal ossification centers of the knee were present, the crown-rump length was 25 cm. or more, and the cervix was ripe. Physicians were more consistent in the selection of patients for elective repeat cesarean section in hospital No. I than in the others. They delivered no immature infants under this circumstance. If there was doubt as to the maturity of the fetus elective cesarean section was usually deferred until the onset of labor. Physicians in hospital No. II observed a similar practice after 1952.

Consultation was always obtained for a cesarean section. It was generally given as agreeing in principle to the operation, however, and not for timing the procedure.

*Causes of Death.*—The cause of death as determined by autopsy examination or clinical observations is given in Table V. Prematurity was the only cause of death of the babies listed under this term. There were no associated maternal complications in these instances. Babies who died of an unknown cause, erythroblastosis, or hyaline membrane were mature. The infant with bronchial obstruction had a plug of mucus in the tracheal tree.

TABLE V. CAUSE OF FETAL DEATH

CAUSE	NO.
Prematurity—anoxia	18
Rupture of uterus—anoxia	17
Congenital anomalies	12
Undetermined	4
Abruptio placentae—anoxia	4
Erythroblastosis	2
Hyaline membrane	2
Toxemia pregnancy—anoxia	1
Bronchial obstruction—anoxia	1
Total	61

We were unable to correlate any significant relationship between the type of anesthesia used and the fetal loss.

### Comment

*Prematurity.*—Nearly 11 per cent of the infants born by repeat cesarean section or following rupture of the uterus were premature. This percentage was greater than for vaginal delivery. Recently Williamson and Winebrenner<sup>15</sup> had a similar experience with repeat abdominal deliveries in one of the medical areas of the United Mine Workers of America Welfare and Retirement Fund. Table VI gives the experience of several clinicians. These figures are not entirely comparable since different periods of time are covered and the cases of uterine rupture are deleted from some statistics. Nevertheless, the table does show that the problem under discussion is common to other communities.

TABLE VI. INCIDENCE OF FETAL LOSS AND PREMATURITY WITH REPEAT ABDOMINAL DELIVERY RECORDED BY DIFFERENT AUTHORS

AUTHORS	NO. ABDOMINAL DELIVERIES	FETAL LOSS (%)	PREMATURITY (%)
Baldwin <sup>1</sup>	616	2.3	6.8
Bryant <sup>2</sup>	1,019*	—	5.0
Bubalo <sup>4</sup>	175	3.9	13.7
Diddle, Gibbs, and Lambeth	934	6.5†	10.7
Erhardt and Gold <sup>8</sup>	6,743	3.0	—
Hall, Kohl, and Schechter <sup>10</sup>	1,597	2.9	11.2
Hess <sup>11</sup>	340	4.1	7.0
Johnston and Morgan <sup>12</sup>	641	2.5	5.7
Wolff and Roter <sup>16</sup>	200	2.5	22.0

\*Ruptures of uterus not included. Other figures are uncorrected.

†Seven and eight-tenths per cent in the first half of the study and 5.2 in the last half of the survey.

As previously described, immaturity of the infant without other apparent complications accounted for nearly a third of the fetal losses. Most of these deaths were in the first 5 years of the study and with elective cesarean section. Hindsight showed that the calculated week of gestation was undependable as a measure of maturity.

*Timing of the Cesarean Section.*—Baldwin<sup>1</sup> observed that the use of roentgenographic study of the fetus was a useful adjunct in determining whether or not the baby was mature. Inconsistent use of the procedure in our community probably stems from two things: (1) Roentgenologists often find that it is difficult to position the pregnant patient properly to obtain satisfactory radiographic studies. (2) Some radiologists frown on the routine use of x-ray studies in pregnancy so that one needs to weigh the value of the procedure in each case.

Labor may be anticipated soon if the cervix is effaced, patulous, and thin. In contrast, an uneffaced, closed, long cervix leads to the opposite opinion. Dieckmann<sup>7</sup> usually disregarded the menstrual age and performed a repeat cesarean section as soon as the vaginal portio disappeared. All of us know that the cervix occasionally ripens before the fetus is mature so that this sign is not entirely reliable as a measure of fetal maturity.

The crown-rump length of the fetus as determined by palpation, in our hands, was as dependable as other measures mentioned. This was true provided obesity or tenseness of the gravid patient's abdominal wall did not preclude its use.

A consultation is desirable both to determine the advisability of the cesarean section itself and for the timing of the procedure. If there is doubt as to the maturity of a fetus, it is advisable to defer the operation even to the point of waiting for the onset of labor. Some prefer to await the onset of labor in all these patients.

*Rupture of the Uterus.*—The main argument for routine elective repeat hysterotomy rests on the threat of rupture of the uterus with possible maternal and fetal death. Sullivan and Campbell<sup>14</sup> and Keymer<sup>13</sup> pointed out that many ruptures take place before the thirty-eighth week of pregnancy after which time most elective repeat sections are recommended. Ruptures, in our experience, appeared as early as the sixth month of gestation and a third of them took place before the thirty-eighth week. Those occurring after the thirty-eighth week were usually more catastrophic, however.

Of the few women previously delivered by cesarean section and allowed to proceed into labor in our community during the last 5 years 2 suffered rupture of the uterus. One rupture was after a classical and the other after



a low-segment section. One woman had to have a hysterectomy immediately post partum because of internal hemorrhage from a partial uterine rupture. The other patient suffered a uterine rupture near the end of labor and required laparotomy. Both parturients and their babies survived.

The present analysis has led us to the belief that the hazard of rupture of the uterus from waiting until the infant is at term is more than offset by the risk of elective delivery of a premature infant. Common sense will have to be used as to whether or not a repeat cesarean section will be selected rather than a vaginal delivery for a maternal complication.

### Summary and Conclusions

The fetal mortality with repeat abdominal delivery was compared to that with primary cesarean section and with vaginal and abdominal deliveries combined in an urban community of East Tennessee for the period 1948 to 1958. The corresponding percentages of fetal losses were 6.5, 10.7, and 3.5 per cent.

Nearly 11 per cent of the babies born by repeat cesarean section or following uterine rupture were premature. This was a higher percentage than for the average vaginal delivery. More than half of the babies born by repeat abdominal delivery died either of prematurity after elective cesarean section or of anoxia in association with a rupture of the uterus.

A decrease in the incidence of premature infants delivered by elective repeat cesarean section and in the number of uterine ruptures accounted for the drop in fetal mortality in the second half of the study as compared with the first half.

It appears that the danger of uterine rupture from waiting until the baby was at term was offset by the risk of elective delivery of a premature baby.

Elective repeat cesarean section is nearly as safe for the baby as vaginal delivery in some hospitals. This is accomplished by careful timing of the operation according to the maturity of the fetus.

The menstrual age was undependable as a measure of determining when a pregnancy was at term. Infants delivered by elective repeat cesarean section were seldom premature if the cervix was effaced, the crown-rump length of the fetus was at least 25 cm. as determined by palpation, and the ossification centers were visible in the fetal epiphyses of the knees as ascertained by radiologic study.

Hindsight indicated that it is usually advisable to defer repeat cesarean section until the onset of spontaneous labor if there is doubt as to the maturity of the baby. Whether or not this procedure should be used routinely would, in our opinion, be dependent on the professional and hospital environment of each institution.

We desire to express our appreciation to Dr. W. B. Farris, Health Department, City of Knoxville, Tennessee, and Miss Sylvia Alberti, Oak Ridge Hospital, Oak Ridge, Tennessee, for their help in this study.

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### Discussion

DR. ROBERT A. COSGROVE, Jersey City, N. J.—Drs. Diddle, Gibbs, and Lambeth describe with precise data the results of a clinical dilemma with which obstetricians will, I believe, be confronted increasingly in the future. Do we or do we not operate upon a woman with a cesarean scar at a predetermined time? Several questions are pertinent:

1. From what does the dilemma arise? Obviously because the woman has a scar from a previous cesarean section. It therefore places a greater burden upon the man who does the primary cesarean than simply the resolution of that particular pregnancy. None of us likes to think that a cesarean done for a questionable indication may be satisfactory at the moment and yet be the cause of disaster in a subsequent pregnancy. We must assure ourselves in each instance that the indication for the first cesarean is valid enough to warrant the strong assumption of maternal or fetal disability and/or death if some other method of delivery is used.

2. Why must a predetermined date be selected? Dr. Diddle's statistics appear convincing that this may be hazardous. It is far better to set a date for evaluation only, rather than definitely for operation. Eleven per cent of the infants were premature and 18 of 40 of these infants died. Further, one third of the ruptures of the uterus occurred before the thirty-eighth week of gestation, the usual time of predetermined operation.

In a recent 8 year period 828 cesareans were done at the Margaret Hague Maternity Hospital on women with a prior cesarean scar. It is our general policy to await the onset of some evidence of labor before making a decision concerning the method of delivery and as a result very few were done at a selected time. Even under such circumstances we lost four out of five infants because of prematurity.

During the same time we lost five infants and one mother because of ruptures of uterine scars. One patient died of renal failure subsequent to massive blood replacement when her uterus ruptured at 24 weeks. The other four ruptures occurred at 35, 38, 39, and 42 weeks, respectively, 2 of the latter before the onset of labor. We are convinced, with Dr. Diddle "that the hazard of rupture of the uterus from waiting until the infant is at term is more than offset by the risk of elective delivery of a premature infant."

3. How is fetal maturity determined? Our policy, of course, acknowledges our inability to estimate such maturity. We grant that an operation done at a time mutually convenient for patient and doctor is often desirable, and in some hospitals may be the only way of preventing an inordinate delay in performing a repeat cesarean section upon a woman who has started labor. We get up at all hours to deliver normal multiparas when they are ready and see no inconsistency in doing the same thing when a woman with a scar and disproportion shows evidence of labor. The infant may still be small if the labor itself starts prematurely, but the operator knows that the woman's time is accomplished and that he is not responsible for such prematurity.

The status of the cervix is unreliable in our experience. I believe the cervix may become effaced some time prior to the spontaneous onset of labor. With other evidence,

however, it may be helpful in confirming an estimate of maturity. Similarly x-ray evidence of ossification is being found to be less absolute and definite than was formerly believed. Reliance on information derived from the menstrual history is so notoriously foolhardy that comment is unnecessary. We have found, as has Dr. Diddle, that the size of the fetus when it can be reasonably determined by palpation and measurement, is usually as reliable as any other evidence. Finally, we are convinced that the most certain evidence of maturity is the onset of labor and are content to handle our own work by a policy of waiting for that time.

DR. DOUGLAS E. CANNELL, Toronto, Ontario.—The improved maternal mortality associated with cesarean section has led in some centers to its performance in approximately 10 per cent of deliveries. The significance of this has been emphasized by Gordon<sup>2</sup>,<sup>3</sup> in two thoughtful and excellent papers. He comments that "the astonishing progress made in reduction of maternal mortality rates and the belief that the perinatal death rate will be similarly lessened by unrestricted abdominal delivery join forces to diminish our fear and increase our complacency. It is of prime importance to remember that the growing incidence of cesarean section is largely due to the pyramiding of this operation as an indication for another."

I should like to comment upon three points among many which this presentation offers for discussion.

1. *Rupture of the Uterus.*—Here, my remarks will be confined to the latter 5 years of Dr. Diddle's study where the incidence of rupture was 1:119. In a recent study of this problem in the Toronto General Hospital, Kumar found 8 ruptures or dehiscences of the uterine incision in 455 repeat cesarean sections over a period of time similar to that considered by Dr. Diddle; of these, 2 were gross symptomatic ruptures, whereas 6 were occult wound dehiscences, noted at the time of repeat cesarean section. The increased incidence of dehiscence as opposed to rupture was noted by Pedowitz and Schwartz<sup>4</sup> and Lane and Reid.<sup>5</sup> In contrast to Lane and Reid, we found no evidence in this small group of patients that the classical, rather than the lower segment, scar withstood labor more satisfactorily. Does Dr. Diddle's incidence of uterine rupture in the last 5 years represent wound dehiscence as well as frank rupture?

2. *Premature Delivery.*—The occurrence of premature delivery and over-all perinatal mortality in the author's review was 10.7 and 6.5 per cent, respectively. Of these a considerable proportion were associated with maternal complications or premature labor. Kumar in our institution found an incidence of prematurity of 5.9 per cent and a gross perinatal mortality of 2.4 per cent. We are in agreement with Jeffcoate's recent statement that "corrected mortality rates are confusing rather than enlightening" and we plan to quote uncorrected rates in the future as being more informative than the corrected rates which are open to the unintentional prejudices of the reporter. Perhaps some difference in management may be the significant factor accounting for the discrepancy in our results as opposed to the author's. In our clinic there has been an increasing tendency to carry the patient to term, or to permit the onset of labor, with the possibility of alternative vaginal delivery, should the circumstances, as noted by Cosgrove,<sup>6</sup> be favorable. This has, in our experience, been attended by a considerable reduction in prematurity and perinatal mortality without an increase in maternal mortality, which was zero in these 455 repeat sections, or an adverse effect upon maternal morbidity.

3. *Limitation of Parity by Cesarean Section.*—One aspect of the increasing employment of cesarean section which was not considered in this presentation was that of the decreased parity of patients delivered abdominally. The report of McNally and Fitzpatrick<sup>7</sup> on patients with four or more cesarean sections indicates that limitation of parity does not necessarily ensue as a result of abdominal delivery. On the other hand, it is our experience that, in fact, it did limit the size of the family, only 10 of our patients having had four or more sections.



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DR. HAROLD S. MORGAN, Lincoln, Neb.—During the 3 years, 1955-1957, a total of 114 cesarean sections were done at the Lincoln General Hospital. Of these, 52 were repeat sections. Of the 52, all were of the low-cervical type and all but two were done under inhalation anesthesia with cyclopropane gas as the anesthetic agent, the average elapsed time between the start of the anesthesia and the delivery of the infant being 8.2 minutes.

No infant deaths were recorded in this small series of repeat sections, whereas in the primary section group, 4 perinatal deaths occurred.

Correlating the period of gestation with the birth weight of the baby we found the following to be significant:

GESTATION	NO.	WEIGHT (GRAMS)
Post term	2	2,832-4,078
273-280 days	12	2,720-4,180
266-273 days	20	2,776-3,820
259-266 days	10	2,522-4,016
252-259 days	2	3,028-3,056
Less than 252 days	6	2,068-2,800

In the 259-266 day group, there was one baby who weighed 4,016 grams. This marked discrepancy between the time of section and the weight of the baby can be accounted for by the fact that the mother had diabetes. In the last group, premature rupture of the membranes, abruptio placentae and misjudging of the gestation period and the size of the baby account for the relatively large number of cases falling into the less than 252 day category.

We are, however, still faced with the fact that 5 of 52 babies were premature. That they survived and were dismissed from the hospital in good condition is probably more to the credit of the pediatrician and the nursing staff than to the obstetrician. It is also of note that all but one of the premature infants fell in the less than 252 day gestation period.

If we are to reduce the neonatal death rate of cesarean section, then we must adhere to the principle enunciated by Dr. Edith Potter during a recent Perinatal Mortality Conference, that the safest time for a baby to be born is between the thirty-ninth and fortieth weeks.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—This paper calls attention to a very important problem in present-day obstetric practice, that is, as the cesarean section rate rises, are we salvaging an increasing number of fetuses or adding new problems of perinatal mortality.

We have come to look upon cesarean section as a mortality-reducing and morbidity-lessening procedure for *both* mother and baby. Perinatal mortality figures, however, indicate that rate of loss in the newborn far exceeds that of vaginal delivery.

This loss is closely linked to difficulties of respiratory physiology which are related to the operation itself. The healthy, vigorous newborn baby, born by cesarean section, can usually empty its respiratory passages of amniotic fluid, gradually expand the alveoli, and finally overcome the handicaps of an abdominal delivery. The premature baby, however, because of its lack of reserve strength and incompleteness of muscular development, often-times has grave difficulty in accomplishing these changes following cesarean section. Air and fluid become mixed in the respiratory passages, inflammatory transudate develops in the alveoli, and soon the fetus forms its own "iron wall" between the oxygen content of respired air and the blood in the pulmonary capillaries.

One of the important considerations therefore at cesarean section, particularly in the case of repeat cesarean section where there is a strong element of election, is to decide when a baby is mature and large enough to survive the procedure of cesarean section.

In our own experience, we cannot rely upon the date of last menstruation, which many of our patients have forgotten or poorly recorded, and which in other cases is unrelated to the period of pregnancy. We have found also that x-ray studies of epiphyseal development lack considerably in accuracy.

Recently we have been resorting to a clinical measurement of the shoulder to rump of the fetus performed with a tape on the surface of the mother's abdomen.

It is usually possible to identify in a head presentation the sulcus between the head and the trunk, placing a zero mark of the centimeter tape on this point and measure over the hemicircumference of the uterus and abdomen to the fundus of the uterus to the fetal rump. We get a measurement of 26 to 28 cm. in an average-sized full-term baby. We have found that this corresponds generally with about a 6½ to 7½ pound baby.

Measurements in the area of 23 to 24 cm. are associated with babies of 4 and 4½ pound size. On the other hand, measurements in the area of 34 to 35 cm. indicate a 10 to 11 pound baby. We have had one measurement of 39 cm. with a baby who weighed 12 pounds and 14 ounces.

We have been accumulating these data and feel that they can soon be published in a scale which will give a pretty accurate clinical estimation of fetal size and may be of considerable help in the resolving of this important problem.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—Recently Dr. Freese and I completed a study of 1,003 term deliveries by cesarean section in which there were no placental and nutritional complications or fetal embarrassment. There were 64 premature infants in addition to the term number. Most of these were in the elective cesarean section group. The premature newborn infants varied in weight from 1,500-2,500 grams. There were 4 deaths in the premature infant group. There were 10 others that had respiratory embarrassment. This occurred whether the mother was in labor or not. This complication occurred in those who had local, gas, and spinal anesthesia.

It was noted that the menstrual history is unreliable for assurance of term age. One must use judgment and clinical calculation to estimate size or full-term development.

In the study mentioned above, all patients with placenta previa, abruptio placentae, toxemia of pregnancy, hypertensive disease, diabetes, etc., and all cases in which there were evidences of fetal embarrassment were excluded from the study. The study was primarily directed to finding the maximum safety factor of cesarean section. The indications for delivery by cesarean section of the 1,003 mothers at term were previous cesarean section (741); previous extensive vaginal surgery (36); dystocia (98); faulty mechanism of labor (21); malpositions of the fetus (46); miscellaneous conditions (40); and medical conditions (21).

Four mothers had twins, which makes a total of 1,007 newborn. The use of anesthesia was as follows: local anesthesia, 56; gas, 113; and spinal, 834. There were 9 fetal deaths in these term babies, 8 of which occurred in the group of patients not in labor and one in labor. All of the deaths were the result of respiratory complications. Labor as such did not exhibit any evidence, either prior or subsequent to delivery, of having any direct influence on the unfavorable outcome. Respiratory embarrassment was found 44 times among those not in labor and only 3 times when labor was in effect. These 3 babies' mothers had gas anesthesia for delivery. Certainly, the influence of labor, if any, was not evidenced in the 139 babies, whereas, in 864 not in labor, there were 8 deaths and an additional 44 had fetal embarrassment.

There are disadvantages and even dangers in waiting for the onset of labor. Our figures, as well as those presented in the paper, seem to indicate that the cesarean section as such is not as safe a procedure as vaginal delivery. The data from Potter of our institution shows that living term babies delivered by the vaginal canal had a fetal loss of only 0.4 of 1 per cent, whereas in our study the fetal loss was 0.9 of 1 per cent. In other words,

vaginal delivery is twice as safe for the fetus as cesarean section. Even so, cesarean section may be lifesaving for both mother and infant. These comments are not condemnation of cesarean section, but rather a strong plea for all of us to sharpen our judgment as to when to do cesarean section, especially the elective operations, and, furthermore, to improve our results in the newborn.

DR. RICHARD BRYANT, Cincinnati, Ohio.—In the last 8 years in Cincinnati, we have had 1,553 repeat cesarean sections. Seventy per cent of these were elective, that is, performed at a predetermined time and date. Five and six-tenths per cent of these babies were premature by weight.

We may be making a slight error in classifying babies as premature who weight 5 pounds, 8 ounces (2,500 grams) or slightly less, if the section is done a week, 10 days, or 2 weeks prior to term. Babies in utero gain up to an ounce a day in the last few weeks of pregnancy, so that the baby who is born 10 days prior to term and weighs 5 pounds, 8 ounces would have weighed 6 pounds or even more had it been allowed to go to term. In other words, the prematurity is more on a statistical basis than an actual fact.

Of the babies delivered by elective cesarean section in the Cincinnati group, there were 6 fetal deaths. Fetal mortality with elective cesarean section perhaps should be defined a little more carefully. In studying fetal loss due to cesarean section, I believe stillbirths should be eliminated from the statistics, because the chances are overwhelming that stillbirth would also have occurred had the patient been delivered vaginally. The same is true of neonatal deaths of babies with anomalies incompatible with life. In our group, and using these criteria, the fetal loss of liveborn babies delivered by elective repeat cesarean section was 0.5 per cent.

There are no figures with which to compare this, for it is no longer possible to give a significant figure for the fetal mortality in vaginal deliveries. The reason is that we no longer deliver large consecutive series of babies vaginally. Thus it may be unfair to compare perinatal mortality in cesarean section with concurrent vaginal delivery statistics, for a significant number of babies who are delivered by elective repeat section and survive would have died—from ruptured uterus, premature separation of the placenta, placenta previa, prolapsed cord, etc.—had vaginal delivery been attempted.

I would like to comment on the inclusion of statistics on ruptured uterus in statistics on cesarean section. I have looked over a dozen textbooks within the last few years—not a single one classifies ruptured uterus as an indication for cesarean section nor is the operation for ruptured uterus called a cesarean section. By definition, I think cesarean section should be the operation in which a baby is removed from an unruptured uterus. I think it is a mistake to include statistics concerning either maternal or fetal results in ruptured uterus with those of cesarean section. Dr. Diddle avoids this error by referring to “abdominal delivery” rather than “cesarean section.”

DR. JOHN R. WOLFF, Chicago, Ill.—In 1955 I reviewed 200 cases of elective repeat cesarean section (*Am. J. Obst. & Gynec.* 69: 1070, 1955). These were all private patients. The results in the babies were somewhat shocking. I found that my associates and I were not at all adept at determining the right time to perform the section. Twenty-two per cent of these infants weighed less than 6 pounds and 5 per cent weighed less than 5 pounds, and 3 babies died during the early neonatal period.

In the attempt to solve such problems the first step, of course, is the recognition of their existence. The essayist has helped us by showing us how we can improve our statistics.

DR. J. BAY JACOBS, Washington, D. C.—In determining the maturity of the fetus in utero, we must consider various factors. The estimated date of confinement should, I think, receive first consideration. The uterus, of course, may appear to be the size of a term pregnancy, but we must consider the amount of amniotic fluid. Just because the uterus is large does not mean that the fetus will be large. In a lateral roentgenogram taken in the standing posture, one can almost always determine the size of the biparietal diameter,



which is a fairly good index of the maturity of the fetus. If the cervix appears to the negotiable, as it would be if favorable for the induction of labor, then we have reason to believe that the patient is just about at term.

A premature infant born after the spontaneous onset of labor stands a much better chance of survival than one that is delivered after induction of labor or by cesarean section.

The patient with an infant of doubtful maturity should not receive any narcotics before she is anesthetized.

DR. DIDDLE (Closing).—Dr. Cannell is correct in interpreting that all the uterine ruptures were in patients who had classical sections.

Drs. Morgan and Montgomery raise the question of anesthesia. In the first 5 years of the study, most of the anesthetics were of the inhalation type. In the last 5 years most were of the regional type. We were unable to show any appreciable relationship between the rate of fetal loss and the type of anesthesia.

Dr. Montgomery raised the question regarding the incidence of prematurity among patients who had normal births. The rate for repeat abdominal delivery was approximately 11 per cent as opposed to 5 to 6 per cent for vaginal delivery.

I suspected beforehand that Dr. Bryant would be critical of the inclusion of ruptured uteri in the study. For this reason the term "repeat abdominal delivery" was used instead of "repeat section." It did not appear fair to talk about the subject without including some of the complications. His remark was well taken, however.

Dr. Bryant also raised the question concerning the actual fetal loss with vaginal delivery. We used a combined figure including both abdominal and vaginal deliveries for the over-all loss. The over-all fetal loss was 3.5 per cent as opposed to 6.5 for repeat abdominal delivery and 10.7 for primary section. I do not remember the rate for vaginal delivery alone.

Like Dr. Cosgrove, I do not feel as competent as Dr. Jacobs in the use of cervical effacement to tell me whether or not the baby is premature or mature.

## FERRODYNAMICS DURING PREGNANCY\*

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**M**ULTIPLE factors are known to be essential for normal erythropoiesis. One of these is iron. Although the morphologic, clinical, and biochemical characteristics of blood during pregnancy have been extensively studied, the various phases of ferrodynamics have received little attention. The processes of iron absorption, excretion, transport, storage, and utilization constitute ferrodynamics since they represent the movement of iron. Investigations on two aspects of iron dynamics were undertaken in an effort to provide answers to several questions. Do women in the reproductive age have normal amounts of storage iron? Is storage iron an "available iron" during pregnancy? Are rates of iron turnover in the plasma and red cell altered during pregnancy? Rath and Finch<sup>1</sup> have demonstrated that by appropriate staining of bone marrow particles an estimate of storage iron can be obtained. By the use of this method it has been possible to study iron storage during pregnancy. Huff, Tobias, and Lawrence<sup>2</sup> have developed a method for determining iron turnover rates. This method has provided useful information about various abnormal hematologic states and in this study has provided data about iron metabolism in pregnancy.

### Methods of Study

All of the patients who were used for these studies were drawn from the Obstetric Service of the University of Nebraska Hospital. Control observations were performed on volunteer medical students, technologists, and stenographers. Only the procedures for measuring storage iron and the radioactive iron studies will be described in detail. Hemoglobin determinations were made by the oxyhemoglobin method with a model DU Beckman spectrophotometer. The Wintrobe tube was used for the hematocrit determinations. The serum iron levels were measured by the method of Barkan and Walker<sup>3</sup> with the use of orthophenanthroline for the color reaction.

It is not difficult to perform a bone marrow biopsy but acceptance of the procedure by the patient is less than satisfactory. Nineteen pregnant women volunteered for this part of the study. The plan of the investigation was to obtain an estimate of storage iron early in pregnancy and then to re-evaluate the stores later in pregnancy under different conditions. Two or three bone

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marrow biopsies were performed on 16 of the 19 patients, on 3 only one storage iron estimate was obtained. Five of the patients received no iron supplement during pregnancy, 4 others received a supplement containing iron and cobalt (Roncovite\*) and a third group of 6 were given 1,000 mg. of intramuscular iron (Imferon†) within 2 weeks of the initial study. The technique consists of obtaining marrow particles by aspiration. The particles are crushed between two glass slides and smeared for staining. A University of Illinois biopsy needle was used for the bone marrow aspiration. The sternum was used for the biopsy because it provides the most accessible red marrow in the adult. After procaine preparation the needle was inserted at a point on the manubrium midway between the first intercostal spaces. Quick suction with a syringe was applied in order to insure removal of bone marrow particulate matter. In addition to the smear prepared for iron staining, a routine smear stained with Wright's stain was made for a morphologic study.

The qualitative estimate of storage iron was made according to the following arbitrary classification:

3+	Excess iron storage
2+	Normal iron storage
1+	Diminished iron storage
Trace	Barely visible iron storage
0	No visible iron storage

The distribution of the stainable iron demands that the entire field in several smears be screened for the final interpretation. Experience gained from the study of stained preparations from normal males and from patients with a variety of hematologic conditions was used in establishing this classification. As a further check on the accuracy of the interpretation, Dr. Peyton Pratt, University of Nebraska Hospital hematologist, independently corroborated the senior author's interpretation.

Seven patients in the last trimester of pregnancy were used for the radioactive iron ( $\text{Fe}^{59}$ ) studies. Control observations were made on 8 normal males and females. In addition, 3 patients, not pregnant, with iron deficiency anemia secondary to chronic blood loss, were studied. The hazards of irradiation in pregnancy are well known, consequently only these few studies have been carried out. We feel that the risks involved are justified to secure needed information. About  $8 \mu\text{c}$  of  $\text{Fe}^{59}$  were incubated for one half hour with the patient's serum and then injected intravenously. The exact amount of isotope administered was calculated from a standard prepared from a measured aliquot of injected dose. Blood was withdrawn for the hemoglobin, hematocrit, and serum iron determinations prior to the isotope injection. Blood samples were drawn at 15, 30, 45, 60, and 120 minutes after the injection for the plasma counts. Additional blood samples were drawn at intervals of 2 or 3 days for whole blood counting until a plateau of red-cell iron utilization had been reached.

All counts are expressed as counts per minute (cpm). Counting was done in a well type scintillation counter with a  $1\frac{1}{2}$  inch sodium iodide crystal (Nuclear of Chicago) and a decade scaler. Duplicate background counts of 5 minutes were obtained before and after each counting period. For counts which were obtained after the day of injection the standard was recounted to calculate decay. Duplicate counts of 5 minutes were obtained on all samples to insure accuracy. Further counts were made if the duplicate values did not agree within a percentage figure based on the formula  $1\sqrt{N}$  where N was the

\*Roncovite, supplied by Lloyd Brothers, Inc., Cincinnati, Ohio.

†Imferon, supplied by Lakeside Laboratories, Inc., Milwaukee, Wis.



approximate counts per minute of the sample being counted. Surface body counts over the liver, spleen, and sacrum were obtained with a Nancy Woods 1 inch straight columnator scintillation counter mounted on a flexible arm. This counter contained a 1 inch crystal. The head of the counter was placed against the skin over the counting site.

A plot of the  $\text{Fe}^{59}$  concentration (counts per minute per milliliter of plasma) against time on semilogarithmic paper produces a straight line which provides the basis for a number of calculations. By extrapolation the zero time concentration was obtained. With this information the plasma and blood volumes were determined from the formulas:

$$(1) \text{ Plasma volume (ml.)} = \frac{\text{cpm injected}}{\text{zero time cpm/ml. of plasma}}$$

$$(2) \text{ Blood volume (ml.)} = \frac{\text{plasma volume}}{(100 - \text{hematocrit})}$$

The significance of the slope of the line can be expressed as the rate constant which is obtained by dividing the natural logarithm of 2 by the half time ( $T/2$ ). The log of 2 is .693 and the  $T/2$  time is defined as the time in hours required to reduce the plasma radioiron concentration to one half of some preceding value. The rate constant is a fraction equivalent to the amount of iron being cleared each hour. The rate constant is more meaningful when applied to the calculation of the plasma iron turnover rate from this formula.

$$(3) \text{ Plasma iron turnover rate (mg./day)} = \frac{.693}{T/2} \times \text{serum iron } (\mu\text{g Fe/ml.}) \\ \times \text{plasma volume (ml.)} \times \text{hours/day}$$

The plasma iron turnover rate is expressed as milligrams per day or may be divided by the body weight and expressed as milligrams per kilogram per day. The value calculated is the amount of iron being cleared by the plasma each day. A fraction is diverted to the marrow where it is incorporated into the red cells. The red-cell iron turnover rate is determined by multiplying the plasma iron turnover rate by the fraction of the tracer which appears in the red cells.

$$(4) \text{ Red-cell iron turnover rate (mg./day)} = \text{plasma iron turnover rate} \\ \times \% \text{ utilization } \text{Fe}^{59}$$

The per cent utilization of  $\text{Fe}^{59}$  is the plateau utilization computed by multiplying cpm per milliliter of whole blood times the blood volume and dividing by the activity of the injected sample. Since normal utilization of  $\text{Fe}^{59}$  approaches 100 per cent in normal subjects, the plasma and red-cell turnover rates are nearly the same.

From the data available the plasma iron pool can be determined by this formula.

$$(5) \text{ Total plasma iron (mg.)} = \frac{\text{plasma volume (ml.)} \times \text{serum iron (mg. \%)}}{100}$$

Another useful expression is the plasma pool turnover rate calculated from the plasma iron turnover rate divided by the total plasma iron. Normal subjects turn over the plasma pool 10 to 18 times per day to provide iron for metabolic requirements.

### Iron Storage and Pregnancy

Biopsies were taken on 12 women between the eighth and fourteenth weeks of gestation. Two of these subjects were young primigravidas; 10 were multigravidas ranging in age from 20 to 41 years. Their hematologic status with

the corresponding storage iron estimate is shown in Table I. These patients may be assumed to be early enough in their pregnancies so that the estimate of their storage iron should be representative of their nonpregnant status. Only one of the 12 patients had normal iron storage and she had received 1,000 mg. of intramuscular iron about a year previous to this study. Six of the group had no storage iron and their hemoglobin ranged from 9.1 to 11.7 Gm. per cent. Five of the patients were shown to have diminished iron stores, either a trace or 1 plus reaction. Clearly, most women enter pregnancy with depleted or partially depleted iron in reserve. It is significant that the patients with iron stores had hemoglobin values above 11.4 Gm. per cent. These observations confirm the impression based on clinical studies that the hemoglobin will remain normal if iron is available, provided that bone marrow function is normal. On the other hand the presence of a normal hemoglobin does not mean that there is iron storage. One patient (A. W.) with a hemoglobin of 11.4 Gm. per cent had no visible iron storage.

TABLE I. STORAGE IRON IN EARLY PREGNANCY

PATIENT	AGE	PARITY	HEMOGLOBIN (GM. %)	HEMATOCRIT (%)	STORAGE IRON
N. S.	24	iv	11.4	36	3+*
B. T.	22	i	13.1	40	1+
M. H.	41	iii	13.1	41	1+
P. M.	20	ii	12.5	39	1+
S. C.	20	iv	12.4	42	Trace
E. K.	17	0	11.7	39	Trace
A. W.	29	vi	11.4	39	0
G. M.	24	v	10.8	36	0
C. H.	18	0	10.1	33	0
R. S.	29	iii	9.6	30	0
M. W.	28	vii	9.3	31	0
A. Y.	26	iv	9.1	33	0

\*Intramuscular iron given during previous pregnancy.

In the plan of investigation 5 patients received no iron supplement over the period of observation. The time interval between studies varied from 84 to 174 days. A comparison of their initial hemoglobin, serum iron, and storage iron values with those obtained late in pregnancy is summarized in Table II. Three of the patients who early in pregnancy had significant amounts of iron in reserve maintained normal hemoglobin and serum iron values through pregnancy. A decrease in the content of the stores was evident in each instance. The 2 patients with but a trace of stainable iron early in pregnancy showed decreases in their hemoglobin values of at least 1 Gm. per cent. In each case the predelivery serum iron was below 60 gamma per cent and all iron reserves had been removed. On the basis of these findings it is evident that storage iron is "available iron" and can be withdrawn for metabolic needs during pregnancy. It is likewise evident that these 5 subjects did not absorb enough iron from their food to meet the demands of pregnancy. No attempt was made to survey their diets in detail. No obvious malnutrition was evident but this type of investigation should be extended to women whose diets have been adequately controlled. The findings suggest that the amount of iron in reserve contributes more to a woman's hematologic status during pregnancy than her dietary intake of iron. In addition, these findings furnish further proof that the concept of physiologic anemia during pregnancy must be abandoned. When adequate storage iron was available there was no anemia. The 2 patients with slight anemia late in pregnancy were truly deficient in iron. Their iron stores were depleted and their serum iron values were in the iron deficiency range.

TABLE II. NO IRON THERAPY. COMPARISON OF STORAGE IRON IN EARLY AND LATE PREGNANCY

PATIENT	STAGE OF PREGNANCY	TIME INTERVAL (DAYS)	AGE	PARITY	HEMO-GLOBIN (GM. %)	SERUM IRON (GAMMA %)	STORAGE IRON
S. C.	Early	174	20	iv	12.4	93	Trace
	Late				10.8	36	0
B. T.	Early	165	22	i	13.1	119	1+
	Late				12.8	89	Trace
M. H.	Early	158	41	iii	13.1	97	1+
	Late				13.4	64	Trace
E. K.	Early	149	17	0	12.2	106	Trace
	Late				11.2	—	0
N. S.	Early	84	24	iv	11.4	84	3+
	Late				11.1	72	1+

A second group of 4 patients was selected to receive an iron and cobalt supplement during their pregnancies. The period of time elapsing between marrow biopsies varied from 63 to 152 days. The iron and cobalt combination was selected because it has, in clinical trials previously reported,<sup>4</sup> proved to be the most effective hematinic for the pregnant woman. The data from the 4 patients are summarized in Table III. Three of the 4 patients receiving iron and cobalt made satisfactory hematologic responses. In each of the 3 the predelivery serum iron was in the normal range. Significantly, each of the patients had absorbed sufficient iron to correct anemia or to maintain a normal hemoglobin while at the same time their marrow stores of iron had increased. The question of whether the addition of cobalt increases iron absorption cannot be answered from these data because, as yet, we do not have information on what iron alone would do. One patient (A. W.) absorbed little or none of the iron. Her hemoglobin decreased slightly and no iron was stored. Either she did not take the iron or failed to absorb it. It has been our experience that an occasional pregnant patient will not absorb iron. The reason for this is not known.

TABLE III. IRON AND COBALT THERAPY. COMPARISON OF STORAGE IRON IN EARLY AND LATE PREGNANCY

PATIENT	STAGE OF PREGNANCY	TIME INTERVAL (DAYS)	AGE	PARITY	HEMO-GLOBIN (GM. %)	SERUM IRON (GAMMA %)	STORAGE IRON
P. M.	Early	133	20	ii	12.5	154	1+
	Late				13.6	100	2+
A. W.	Early	152	29	vi	11.4	40	0
	Late				10.6	13	0
M. W.	Early	63	28	vii	9.3	44	0
	Late				11.6	127	Trace
R. S.	Early	98	29	iii	9.6	57	0
	Late				11.0	100	1+

A third group of 6 patients received 1,000 mg. of intramuscular iron. The data from these patients are summarized in Table IV. Two of the group (Nos. 1 and 2) were examined early in pregnancy and were found to be moderately anemic. Their bone marrow showed no storage iron. A gram of intramuscular iron was given and failed to produce a response. Late in pregnancy the administered iron was present in storage for 1 plus and 2 plus reactions were demonstrated. Morphologic study of these marrows revealed hypocellularity indicating the possibility that these patients had only partially responsive bone marrow. The anemia was hypoplastic in type and not the result of iron deficiency. In an unpublished series of 75 women given intramuscular iron other



examples of failure to respond have been noted. A third patient (K. C.) received intramuscular iron early in pregnancy but only a predelivery bone marrow biopsy was obtained. Her response to the iron was satisfactory and the storage iron was estimated at 1 plus. These findings would suggest that the administration of 1,000 mg. of iron intramuscularly during pregnancy does not lead to an excess of body iron. Two patients with moderate anemia were first examined late in pregnancy. Storage iron was absent. A gram of intramuscular iron produced a response in one patient (No. 5) but failed in the second (No. 4). In both patients' bone marrow iron appeared after the iron injections. The last patient (No. 6) was admitted in labor with marked iron deficiency anemia. Five days after the first injection of intramuscular iron a trace of bone marrow iron was visible. Only a fraction of the iron in the depots had been released in this short period. The high serum iron noted on the fifth day is characteristic and may persist for several days after the last intramuscular injection. The patient responded nicely but further marrow biopsies were refused.

TABLE IV. INTRAMUSCULAR IRON THERAPY. COMPARISON OF STORAGE IRON IN EARLY AND LATE PREGNANCY. EACH PATIENT RECEIVED 1 GM. OF INTRAMUSCULAR IRON

PATIENT	STAGE OF PREGNANCY	TIME INTERVAL (DAYS)	AGE	PARITY	HEMO-GLOBIN (GM. %)	SERUM IRON (GAMMA %)	STORAGE IRON
A. Y.	Early		26	iv	9.1	128	0
	Late	147			8.6	64	1+
G. M.	Early		24	v	10.8	64	0
	Late	98			9.6	50	2+
K. C.	Early		30	v	11.0	60	—
	Late	159			11.6	64	1+
B. H.	Late		29	viii	9.7	30	0
	Late	39			9.8	145	2+
	Post partum	86			10.7	80	1+
B. N.	Late		19	iii	10.1	64	0
	Late	28			11.7	68	1+
	Post partum	73			12.3	44	3+
V. J.	Labor		32	viii	8.1	28	0
	Post partum	5			8.1	462	Trace
	Post partum	47			11.7	80	—

TABLE V. ANEMIA OF INFECTION. NO IRON THERAPY ADMINISTERED

PATIENT	DIAGNOSIS	TIME INTERVAL (DAYS)	AGE	PARITY	HEMO-GLOBIN (GM. %)	SERUM IRON (GAMMA %)	STORAGE IRON
G. D.	Pyelonephritis		22	iv	9.8	20	3+
		41			12.3	28	Trace
		142			12.8	60	0
S. D.	Pyelonephritis		16	i	6.4	20	1+
		84			9.4	20	0

Two other patients of special interest have been investigated. The findings in these cases are shown in Table V. Each of these patients was admitted to the hospital for treatment of chronic pyelitis. The anemia was secondary to the infection and was characterized by 1 plus and 3 plus marrow iron reactions, a low iron-binding capacity of the serum, and a remission of the anemia following antibiotic therapy. Neither of the patients received iron therapy. It is of

interest to note the mobilization of the storage iron for hemoglobin repair after the block to synthesis has been removed. Patient G. D. exhibited 3 plus marrow iron. Her hemoglobin rose to 12.3 and 12.8 Gm. per cent without iron therapy while over the 20 weeks of observation her iron reserves were depleted. The second patient showed a similar mobilization of iron reserves for repair. She should have received additional iron but was lost to our study at this point. These findings illustrate again that storage iron is "available iron." Infection is often overlooked as a cause of anemia during pregnancy.

In summary, these studies on storage iron emphasize the importance of storage iron for hematopoiesis in pregnancy. The demands for iron by the fetus and by the mother for extra hemoglobin synthesis are in excess of that which can be supplied by the diet alone. Storage iron is "available iron" and can be mobilized for the fetal requirement or for maternal hemoglobin production. Diet supplementation with iron and cobalt provides the necessary iron to maintain a normal hemoglobin. It remains to be shown whether iron alone will do this. The evidence that 11 of the 12 pregnant women investigated early in their pregnancies had deficient stores provides us with the rationale for routine diet supplementation with iron during pregnancy. The female exists in a precarious state of iron balance principally because of iron loss through menstruation and pregnancy. Iron alone is not the only factor responsible for normal erythropoiesis. The demonstration that adequate iron stores provided by intramuscular iron injection failed to elicit a response can be explained only by bone marrow failure to use the available iron.

#### Plasma and Red-Cell Turnover Rates

Seven patients were investigated by the radioiron method in the last trimester of pregnancy. Four of the 7 were reasonably normal with respect to their hematologic status though bordering on iron deficiency. Three of the patients had iron deficiency anemia. For comparison normal subjects and patients with iron deficiency anemia secondary to chronic blood loss were studied.

$T/2$  times, the plasma iron pool, the number of times this pool was turned over, the plasma iron turnover rates, the per cent utilization of  $Fe^{59}$  by the red cells and the red-cell iron turnover rates for the pregnant patients, normal subjects, and nonpregnant patients with iron deficiency anemia are shown in Tables VI and VII.

The half time values ( $T/2$ ) were within the normal range for the 4 patients with the highest hemoglobin levels and were decreased in association with marked anemia. The direction of the change is consistent with the more rapid  $Fe^{59}$  clearance found in the iron deficient controls. The total amount of plasma iron was decreased in all the pregnant patients, markedly so in those with anemia. The plasma iron turnover rates were similarly decreased in pregnancy, more so than determined for the iron deficient controls. In the anemic pregnant subjects the pools of plasma iron turned over 19 to 23 times a day which was typical of iron deficiency. All of these observed changes in plasma iron kinetics are consistent with those established for iron deficiency states.

Red-cell utilization of  $Fe^{59}$  varied between 81 and 97 per cent during pregnancy. The mean value (90 per cent) is slightly lower than observed in the normal subjects. This is not surprising since a small fraction of the radioiron is diverted to the fetus. The red-cell iron turnover rates for pregnancy were all markedly reduced. It was anticipated that pregnant subjects with normal hematologic levels would exhibit increased rates because of their greater hemoglobin mass and the necessity for producing larger quantities of hemoglobin.

TABLE VI. PLASMA IRON TURNOVER DATA IN NORMAL SUBJECTS, NONPREGNANT PATIENTS WITH IRON DEFICIENCY ANEMIA, AND PREGNANT PATIENTS

PATIENT	T/2 TIME (HOURS)	PLASMA IRON POOL (MG.)	PLASMA IRON TURNOVER RATE (MG./KG./DAY)	NO. OF TIMES/DAY PLASMA POOL TURNED OVER	HEMO- GLOBIN (GM. %)	HEMA- TOCRIT (%)	SERUM IRON (GAMMA %)
<i>Normal Subjects.—</i>							
Mean	1.27	3.0	.50	12.8	14.5	46	115
Range	.94-1.58	2.1-4.0	.35-.59	9.5-17.9	12.1-16.1	41-50	86-160
<i>Iron Deficiency Anemia.—</i>							
Mean	.53	1.1	.38	19.1	7.3	29	17
Range	.38-.62	.8-1.4	.32-.46	16-25	6.4-8.1	27-30	13-21
J. A.	1.26	1.5	.28	13.2	11.1	35	57
D. W.	1.00	1.0	.26	16.7	11.2	34	41
N. G.	1.13	1.4	.36	14.7	11.1	35	55
E. H.	1.53	1.8	.27	10.9	11.1	35	79
G. H.	.75	.7	.26	23.0	8.6	30	17
G. K.	.88	.4	.14	18.8	7.2	28	13
N. W.	.78	.6	.25	22.0	7.5	27	23

TABLE VII. RED-CELL IRON TURNOVER DATA IN NORMAL SUBJECTS, NONPREGNANT PATIENTS WITH IRON DEFICIENCY ANEMIA, AND PREGNANT PATIENTS

PATIENT	MEAN MAXIMUM $Fe^{59}$ UPTAKE (%)	RED-CELL IRON TURNOVER RATE (MG./KG./DAY)
<i>Normal Subjects.—</i>		
Mean	94	.47
Range	88 - 102	.33 - .53
<i>Iron Deficiency Anemia.—</i>		
Mean	99	.37
Range	95 - 104	.33 - .44
J. A.	86	.24
D. W.	89	.23
N. G.	81	.29
E. H.	91	.25
G. H.	91	.24
G. K.	93	.13
N. W.	97	.24

A simple interpretation of these data would be iron deficiency. The rate constant  $\left(\frac{\log 2}{T/2}\right)$  was normal or increased in the pregnant subjects. The plasma clearance rate was thus normal or increased. The plasma iron turnover rate obviously was reduced because of the low serum iron and small plasma iron pool. Two other explanations must be considered, however. The iron in the plasma is bound to a metal combining protein. Previous studies<sup>5</sup> have demonstrated that the amount of iron-binding protein is increased during pregnancy. The observed changes could be explained on a more rigid binding of the iron. A second explanation would involve the red-cell production rate. The low red-cell iron turnover rate, particularly in the 4 pregnant patients with hemoglobin of around 11 Gm. per cent, could be explained by a depressed production rate of erythrocytes. This theory becomes more tenable when red-cell  $Fe^{59}$  utilization is considered in terms of the time necessary for complete utilization and when body surface counts are considered. The normal subject utilizes the tracer of  $Fe^{59}$  in 7 to 10 days and in iron deficiency the time required has varied from 3 to 5 days. These pregnant patients "plateaued" in 10 to 14 days in



spite of the fact that 3 of the group were markedly iron deficient. Body surface counts are illustrated in Figs. 1 and 2. A difference between the normal and pregnant patients was demonstrated for the liver counts. When the large amount of tissue being monitored in the liver scan by comparison with the sacrum is considered the high liver counts become more significant. This finding is best explained by bone marrow depression, or in other words a bone marrow hypoplasia. The iron cleared by the plasma cannot be accepted by the marrow because erythrocyte production is relatively slowed. The iron is diverted to the liver and is held in a labile pool from which it is slowly withdrawn for red-cell production.

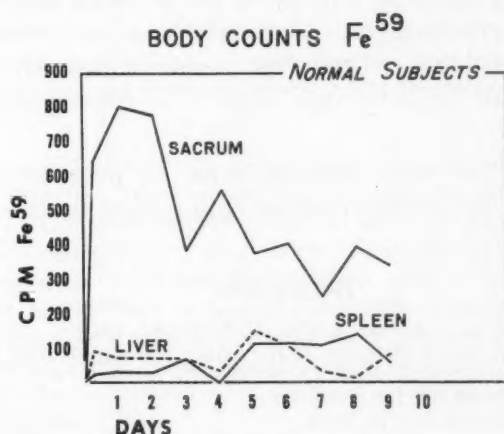


Fig. 1.—Body surface counts on normal subjects who have received approximately 8  $\mu$ c of  $\text{Fe}^{59}$ .

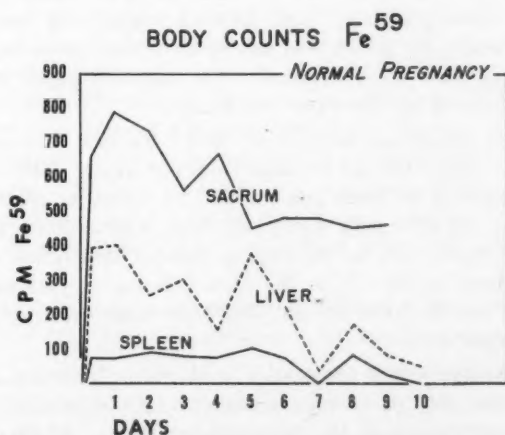


Fig. 2.—Body surface counts on pregnant subjects who have received approximately 8  $\mu$ c of  $\text{Fe}^{59}$ .

### Summary and Conclusions

Two phases of ferrodynamics have been investigated. Storage iron estimates were made on 19 pregnant women from which certain conclusions are warranted.

1. Storage iron depots are reduced in the majority of women at the onset of pregnancy.

2. Storage iron is "available iron" and can be utilized to satisfy the iron demands created by pregnancy.

3. Iron from the diet is probably not sufficient to meet the iron requirements imposed by pregnancy and an iron supplement should be routinely provided.

Radioiron studies were performed on 7 patients, 3 of whom exhibited iron deficiency anemia of pregnancy. Plasma iron turnover rates are decreased during pregnancy. A similar reduction in the red-cell iron turnover rate was observed. These findings could be explained on the basis of iron deficiency. A theory postulating a retarded red-cell production rate was advanced. The theory was based on the low red-cell iron turnover rate, the retarded red-cell utilization of  $\text{Fe}^{59}$ , and the relatively high liver counts obtained by surface scanning.

Iron deficiency is the most common cause of pregnancy anemia. There apparently is some degree of bone marrow suppression in association with pregnancy.

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### Discussion

DR. CURTIS J. LUND, Rochester, N. Y.—The ancient *Ebers Papyrus* describes the proper use of naturally occurring salts of iron such as oxides and carbonates, as internal remedies. Since then limitless time, effort, and money have been spent to unravel the function and use of a pennyworth of this common metal. The splendid paper which we have heard characterizes Dr. Holly as one of our foremost "iron men."

We must realize that important studies of this type are time consuming and technically very difficult. The quantities to be measured are small. The total iron content of the average pregnant woman is no more than 4 Gm. or about as much as is found in the common eight penny nail. Of this only 0.001 per cent, approximately 4 mg., is found in the plasma. For this reason, as well as for others, plasma iron levels are not as meaningful as we once thought them to be. It is the iron balance or exchange of iron between the plasma, the erythrocytes, and the stores, the bone marrow, liver, and spleen, which provides more useful information.

I agree that many women enter pregnancy with some depletion of storage iron, but one might question measurements of storage made during the twelfth or fourteenth week of gestation as being representative of the nonpregnant state. At this period of gestation we have observed significant increases in the total circulating hemoglobin mass. Some of the iron for this expansion undoubtedly comes from the stores, as the capricious diets of early pregnancy are notoriously poor in iron. Nevertheless, the data presented clearly indicate that the storage of iron in the bone marrow may be low during early pregnancy. The data do not indicate the condition of the stores in the liver and the spleen. The curve of  $\text{Fe}^{59}$  uptake by the liver is similar to that of the marrow and suggests that the liver may contain a large pool of labile iron associated with the increasing quantities of ferritin which it produces during pregnancy.

An alternative was suggested that the high liver counts might represent an accumulation of iron due to failure of utilization by hypoplastic bone marrow. Is this likely in the presence of low serum iron, histologic evidence of diminished iron stores in the stained

marrow, and the characteristic hyperplasia so long described as typical of pregnancy? If in addition to this there is the customary increase in total circulating hemoglobin mass then I would doubt the presence of hypoplasia of the marrow regardless of the rate of erythrocyte iron turnover and the high content of iron in the liver. Were bone marrow studies done on the patients who received Fe<sup>59</sup>?

Have we not lost sight of the largest reservoir of iron—the hemoglobin of the erythrocyte? During pregnancy much of the ingested iron and some of the storage iron is utilized in the production of a large hemoglobin mass, a mass which often appears to be in excess of the increased requirements of pregnancy for oxygen-carrying capacity. In the absence of hemorrhage or hemolysis this iron will be released from the blood during the puerperium to return to the stores in the marrow, liver, and spleen. In this manner the pregnant woman may successfully complete a pregnancy without anemia but with very little iron to be found in the fixed depots. I agree that this is a precarious situation which cannot be condoned and need not occur under proper preconceptional and prenatal therapy.

DR. NEWLIN FELL PAXSON, Philadelphia, Pa.—Dr. Holly stresses an important basic fact that storage iron is available iron provided the bone marrow is functioning normally. It is utilized during pregnancy so that the store is diminished or depleted unless iron is given by supplementary medication. Oral iron and cobalt and intramuscular iron both produced increase in hemoglobin levels but in one case iron and cobalt produced no change in either storage iron or hemoglobin levels, suggesting deficient bone marrow function. In 2 patients who received intramuscular iron there was a drop in the hemoglobin level in spite of a rise in the storage iron level, suggesting either defective bone marrow function or that iron alone may not be the best hematinic. These observations need further investigation.

Dr. Holly offers a theory that seems logical in the light of present knowledge, that there is a depressed production rate of red cells in pregnancy anemia. Iron cleared by the plasma cannot be accepted by the bone marrow because erythrocyte production is relatively slowed. The iron is then diverted to the liver as a labile pool.

Abandonment of the concept that the physiological anemia of pregnancy is due to hemodilution is a definite step forward in pregnancy physiology and should be emphasized, since some of the most recent textbooks on obstetrics still describe hemodilution as the normal cause of low hemoglobin and hematocrit levels. Nevertheless, the fact that some hemodilution does occur in pregnancy must be recognized.

Important as Dr. Holly's studies in iron metabolism are, the importance of protein metabolism also should be remembered in considering pregnancy anemia and, as this paper indicates, an adequate diet needs to be defined that will maintain a normal level of storage iron.

Another fact that might be investigated further is the definition of the normal level for storage iron. Is 4 plus a normal level or a saturation capacity? Perhaps 1 plus might be the normal.

DR. HOLLY (Closing).—Dr. Lund commented on the fact that we were here studying bone marrow iron but used it to represent storage iron. It is impossible in the human to perform a biopsy on the liver or spleen under most circumstances. We have carried out exhaustive studies on animals, as have others, which have shown that bone marrow stainable iron is a true index of iron storage. We make the assumption that what we find in the bone marrow is similar to that which we would find in the liver and spleen.

You have commented on the discrepancy between previous reports of bone marrow "hyperplasia" and the use of the term "hypoplasia" in this discussion. I think the nomenclature is a little confusing for we do not differentiate between the histologic appearance of the marrow which is usually a hyperplasia and the red-cell production rate which may be relatively diminished during pregnancy. The two concepts are compatible in my mind. As an example, a nonpregnant individual with aplastic or hypoplastic anemia may have a hyperplastic marrow with a marked decrease in red-cell production.



You have asked about the marrows of the patients who had the  $\text{Fe}^{59}$  studies. One of these patients was examined and no iron was demonstrated. I am certain that other factors enter into erythrocyte production. We are currently studying the iron-binding properties of pregnancy plasma. The iron-binding protein is a specific protein fraction and is increased in nearly all pregnant women. The only examples of a decrease, incidentally, occur in the patients with anemia of infection and the test is diagnostic for this type of anemia. The increase in iron-binding protein during pregnancy is well known but it may well be that our interpretation of the radioactive iron data may be changed if we find that iron-binding properties are different during pregnancy.

Dr. Paxson has raised the question of hemodilution. Certainly hemodilution does occur or at least the plasma volume increases during pregnancy. The point I would like to make is that if there is iron available and if marrow function is normal, the body has the capacity to manufacture red cells and hemoglobin which is equal to the plasma volume increase. Hemodilution (anemia is a better term) becomes apparent only if there is an iron deficiency or decreased marrow production of red cells.

The diet was mentioned. The diet, of course, plays an important part but I am convinced that the diet is more important for substances it contains which assist in the absorption of iron rather than for its iron content. Our diets are poor in iron. I should mention one clan of the Bantu tribe which has been extensively studied. Whereas our diets may contain from 7 to 10 mg. of iron per day, these Bantus live on a diet which contains nearly 200 mg. of iron per day. In one study it was found that anemia did not occur in their pregnant women.

## SERIAL STUDIES OF SERUM LIPIDS IN NORMAL HUMAN PREGNANCY\*

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IN RECENT years, much attention has been focused upon the production of arterial and arteriolar thickening, the deposition of atheromatous plaques in vessels, and the eventual production of hypertension. These features have further attracted attention in attempts to establish possible relationships between cholesterol metabolism and the ultimate development of atherosclerosis. In the pregnant patient, the spheres of obvious interest revolve about the relationship between atherosclerosis and the so-called hypertensive disorders of pregnancy, particularly pre-eclampsia-eclampsia. In addition to the features relating to circulatory and blood pressure changes during pregnancy, it is known that high concentrations of many of the steroids occur as normal pregnancy advances. Since cholesterol is the source of most of the steroids found in increased amounts in the circulation of normal pregnant patients, the part played by lipid metabolism in pregnancy, both normal and abnormal, becomes all the more intriguing.

It has been known for years that an increase in circulating lipids occurs during pregnancy. Even though cholesterol and other lipid substances have been the center of considerable lay interest and also the subject of much scientific investigation, relatively few reports have dealt with serial studies of lipids during pregnancy. Based upon virtually no information, Becquerel and Rodier<sup>1</sup> in 1845 suggested that hyperlipemia occurred during pregnancy. They hypothesized that this change represented an increase in blood cholesterol as well as an increase in lipid phosphorus during pregnancy. Two years later Virchow<sup>2</sup> showed that the milky appearance of sera of some pregnant women was due to the presence of fat; this was demonstrated by shaking the sera with ether so that the fat could be extracted. Many of the early investigators felt that the hyperlipemia of pregnancy probably occurred as a result of increased fat absorption, poorly assimilated chyle, or from the mixing of milk with blood for the nourishment of the fetus.

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The first chemical study was undertaken in 1911 when Chauffard and associates<sup>3</sup> demonstrated an increase in blood cholesterol during pregnancy. In the same year Neumann and Herrmann<sup>4</sup> studied the lipid partitions in 5 L. of pooled whole blood obtained from various patients during *the fourth stage of labor*. The development of micromethods made it possible to study blood lipid partitions accurately. This innovation led to some diversity of opinion as to which lipid fractions were grossly changed during pregnancy. The only general agreement was that an increase in total cholesterol and in neutral fat occurred during pregnancy. It was not until the epochal paper of Boyd<sup>5</sup> in 1934 that the principal cause for the widely divergent results reported before that time was found to be the fact that some investigators were reporting determinations performed on whole blood, while other reports were based upon investigation of plasma and serum specimens. Dieckmann's<sup>6</sup> report in the same year dealt only with plasma cholesterol. Boyd found that almost no change occurred in the lipid content of red blood cells during pregnancy. However, striking changes were noted in the plasma lipids. The most pronounced change was an increase of greater than 100 per cent in plasma neutral fat and a 25 per cent increase in plasma phospholipid and free cholesterol at term. Ever since his report, all investigation has been focused on plasma and serum lipids rather than on whole blood studies.

Lipids embrace an enormous area and the term has recently been applied to define all fats and fatlike substances. Lipids include all substances which are insoluble in water but which are: (1) soluble in the so-called fat solvents (diethylether, petroleum ether, chloroform, hot alcohol, benzene, carbon tetrachloride, acetone, etc.); (2) related actually or potentially to fatty acid esters; (3) utilized by the animal organism. The latter criterion excludes the mineral oil derivatives from the class of lipids. Certain compounds included as lipids, such as lecithins, cephalins, cerebrosides, and sphingomyelins, are not soluble in all the above solvents. Thus, the criteria for inclusion within the general class of lipids are somewhat flexible. The blood lipids thus consist of fatty acids, neutral fats, phospholipids, and unsaponifiable components including cholesterol, carotenoids, vitamins A, D, E, and K, as well as other substances in relatively small amounts. Cholesterol, phospholipids, carotene, etc., are carried in the blood almost exclusively in the form of lipoproteins, whereas neutral fats are carried chiefly in the form of chylomicrons, which may, in turn, be stabilized by protein films. The fatty acids occur in combination with the phospholipids, in ester combination with cholesterol, and with the carotenols and fat-soluble vitamins. Fatty acids are also bound to plasma proteins, the latter fraction probably being identical with that referred to as free fatty acids.

### Materials

The present report will concern itself with a discussion of the changes in total lipids, total serum cholesterol, ester cholesterol, free cholesterol, phospholipids, and lipid phosphorus during normal pregnancy. In this way baseline values and trends may be established in the normal pregnant patient for comparison with the changes noted in the various abnormalities of pregnancy.



Even though simultaneous studies of lipoprotein distributions were performed, the vastness of this area precludes their detailed recording in this communication but will form the subject of an additional publication. However, the relationship between the lipid fractions described herein and the lipoproteins will form a part of the present report.

Inasmuch as there may be even minor differences in technique and experimental design in various institutions dealing with the same problem, we felt it desirable to establish our own control group of normal nonpregnant women rather than to make comparisons with other reports. Our control group consisted of 15 normal nonpregnant women ranging in age from 20 to 43 years. Twelve were members of our technologic and research staff; the remaining 3 individuals were patients on our service with minimal problems which were not related to pregnancy or to defects in lipid metabolism.

The experimental group consisted of 25 normal pregnant patients drawn from approximately the same nonindigent economic and social level. All patients received the same antepartum advice and prenatal care. All pregnancies were normal; no patient was included if any abnormality subsequently occurred during the pregnancy. In 10 patients of the experimental group all lipid studies and determinations were performed serially at approximately monthly intervals throughout the pregnancy. This group is called the "Serial Group." These patients were followed for varying lengths of time throughout the pregnancy, depending upon the stage of pregnancy at which they first reported to the prenatal clinic. One patient, a laboratory technician who had volunteered to serve as a nonpregnant control, was in the fifth week of her pregnancy before the diagnosis was suspected. She was then followed at the same frequent intervals throughout the pregnancy, delivery, and early and late postpartum periods. Thus, an opportunity was provided to study the serial changes in lipid distribution in pregnancy, as related to the nonpregnant control level in the same patient as well as in the larger group. The complete data on this patient have been reported recently.<sup>52</sup>

On the remaining 15 patients, "spot" determinations were performed at varying times during the pregnancy. Even among this group as many as 3 or 4 determinations were performed during the same pregnancy. In addition to the determinations carried out prior to delivery the same lipids and fractions were measured during the first 6 postpartum days on 10 patients and at approximately 6 to 7 weeks post partum on 8 patients.

### Methods

Total lipids, total cholesterol, ester cholesterol, free cholesterol, and phospholipids were determined, with the use of serum samples. All blood was drawn in the morning before breakfast following a fasting period of at least 12 hours. In this way, fluctuating lipid levels following meals were minimized. Although the majority of the studies were terminated at approximately 6 to 7 weeks post partum, the one patient serially followed from the fifth week of pregnancy<sup>52</sup> had postpartum determinations at 9 hours, 4 days, 7 weeks, 15 weeks, and 6 months, in addition to those performed throughout her pregnancy. Total lipids were determined according to the method of Sperry and Brand.<sup>7</sup> Lipid phosphorus was determined according to the method of Youngburg and Youngburg,<sup>8</sup> with the phosphorus procedure of Fiske and Subbarow.<sup>9</sup> Total and free serum cholesterol was determined by the Sperry and Webb<sup>10</sup> modification of the Schoenheimer and Sperry<sup>11</sup> procedure and further modified by our Department of Pathology.<sup>12</sup> Lipoprotein distribution was determined as described by Jencks and associates,<sup>13, 14, 15</sup> with a Spinco Model R Series B cell and oil red O in 60 per cent ethanol as the lipid stain.

All data were grouped according to the duration of pregnancy in lunar months. Statistical treatment of the data for each group included calculations of the mean, standard deviation, and standard error of the mean. Statistical analyses also included testing the means to determine whether differences in the means were real or whether such differences occurred as a result of chance. The "t" test was used to determine the significance of the difference of the means.

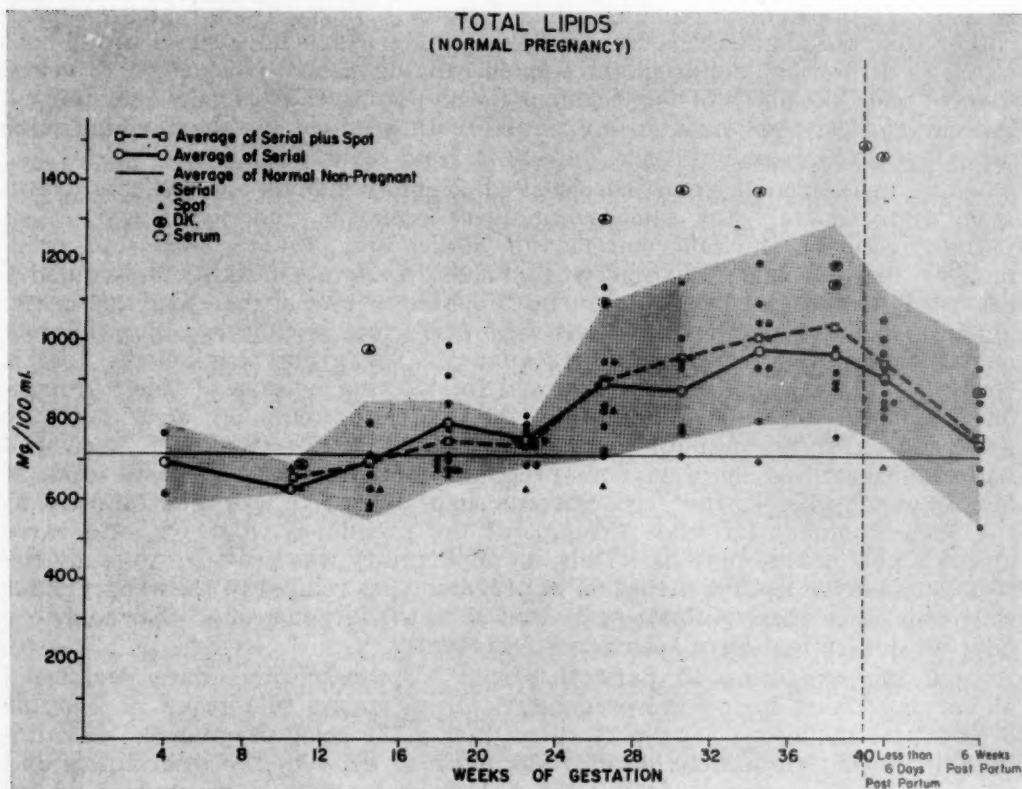


Fig. 1.—Total serum lipids determined during normal pregnancy. The solid line represents the mean of the group of patients upon whom serial determinations were made through pregnancy. The dotted line represents the average of the serial and "spot" patients. The standard deviation for the entire group is represented by the shaded area.

TABLE I. SERUM TOTAL LIPIDS IN NORMAL PREGNANCY

	NO. DETERMI- NATIONS	MEAN (MG./100 ML.)	STANDARD DEVIATION (MG./100 ML.)	PROBABILITY	% OF CONTROL
Control	20	711	139		100
0-8 weeks	2	688	105	N. S.	97
9-12 weeks	4	653	33	N. S.	92
13-16 weeks	8	694	148	N. S.	98
17-20 weeks	13	745	105	N. S.	105
21-24 weeks	10	737	55	N. S.	104
25-28 weeks	12	900	198	<0.01	127
29-32 weeks	9	964	208	<0.001	136
33-36 weeks	10	1018	194	<0.001	143
37-40 weeks	8	1039	238	<0.001	146
1-6 days post partum	12	940	195	<0.001	132
6-7 weeks post partum	8	761	232	<0.02	107

### Results

**Total Lipids.**—Serial determinations of total lipids are noted in Table I and in Figs. 1 and 2. Even though a mild depression in total lipids occurs at the twelfth week of pregnancy as compared with the normal nonpregnant control, this difference is not statistically significant. Significant elevation of the total lipids does not occur until after the twenty-fourth week of gestation, following which a rapid elevation occurs and persists until term. The

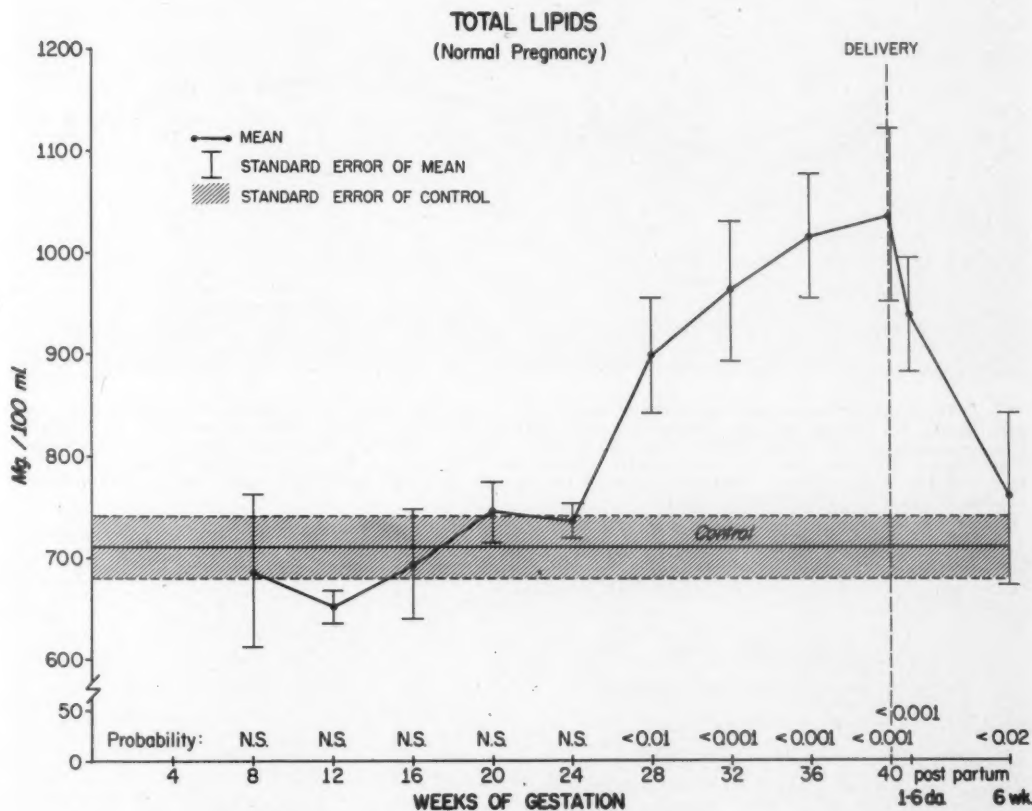


Fig. 2.—Total serum lipids determined during normal pregnancy. All determinations are divided into groupings by lunar months ante partum, and into early and late postpartum groups. The solid curve represents the means of these groupings, and the vertical lines the standard error of each mean. The control group is composed of young, nonpregnant women. The shaded area represents the standard error of the control mean.

maximum value is reached during the tenth lunar month at which point the concentration of total lipids has risen to 146 per cent of that of the control mean, not only of the normal nonpregnant group, but also as compared to the level during early pregnancy. A decline of minimal degree is present during the first 6 postpartum days. It is interesting to note that by the sixth week post partum total lipid concentration has further decreased toward normal, but is still increased above the normal control level to a statistically significant degree. Throughout pregnancy the calculated standard deviation is noted to be quite large, indicating the wide range of values found.

**Cholesterol.**—Total serum cholesterol is depicted in Figs. 3 and 6 and the means and standard deviations are shown in Table II. As with the total lipids, no statistically significant changes from the control group are noted until after



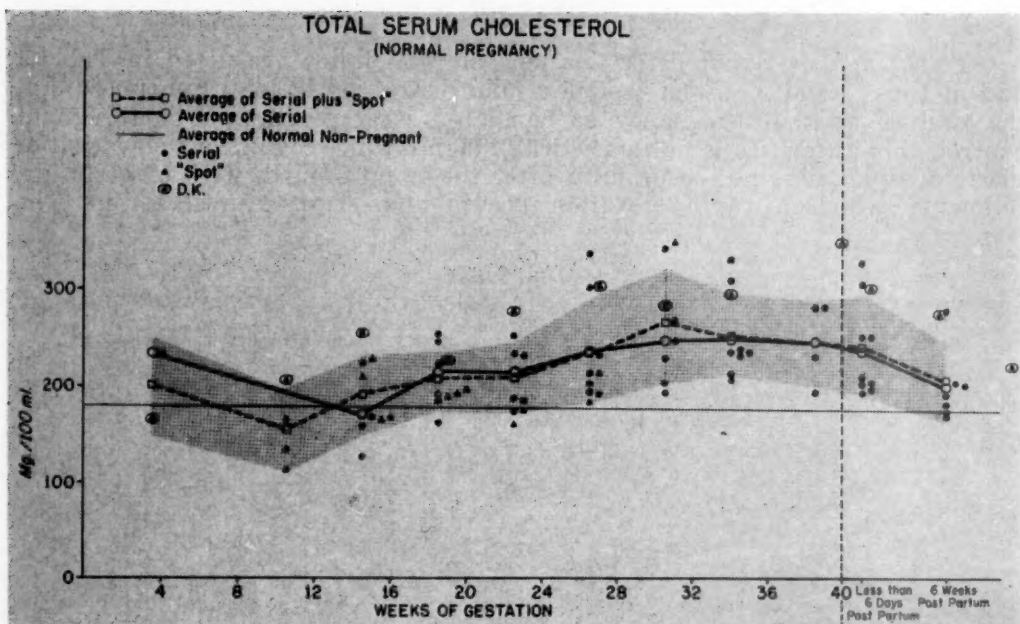


Fig. 3.—Total serum cholesterol determined during normal pregnancy. The solid line represents the mean of the group of patients upon whom serial determinations were made through pregnancy. The dotted line represents the average of the serial and "spot" patients. The standard deviation for the entire group is represented by the shaded area. "D. K." is a patient upon whom determinations were made serially from the fifth week of gestation through the late postpartum period.

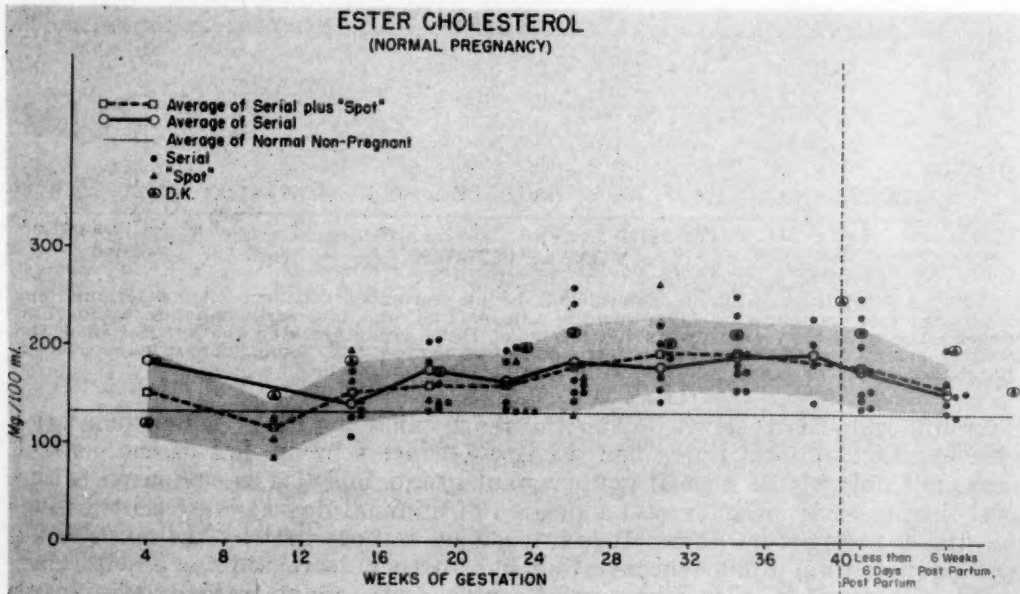


Fig. 4.—Serum ester cholesterol determined during normal pregnancy. The solid line represents the mean of the group of patients upon whom serial determinations were made through pregnancy. The dotted line represents the average of the serial and "spot" patients. The standard deviation for the entire group is represented by the shaded area. "D. K." is a patient upon whom determinations were made serially from the fifth week of gestation through the late postpartum period.

the sixteenth week of pregnancy. While there is a trend toward an early increase in total cholesterol concentration beginning at the sixteenth week, these differences are not statistically significant until the twentieth week of pregnancy. The increase in total cholesterol is gradual, reaching its height at the thirty-seventh week with a very slight decline continuing to term but still remaining markedly elevated as compared to the control group. The decline in total cholesterol during the first six postpartum days is not nearly so pronounced as the depression of total lipids. By the sixth to the seventh week post partum, a further decrease in total cholesterol concentration has occurred but not to the level of the control group nor to the concentration noted during early pregnancy. During the eighth lunar month, total cholesterol reached a maximum of 149 per cent above the control level.

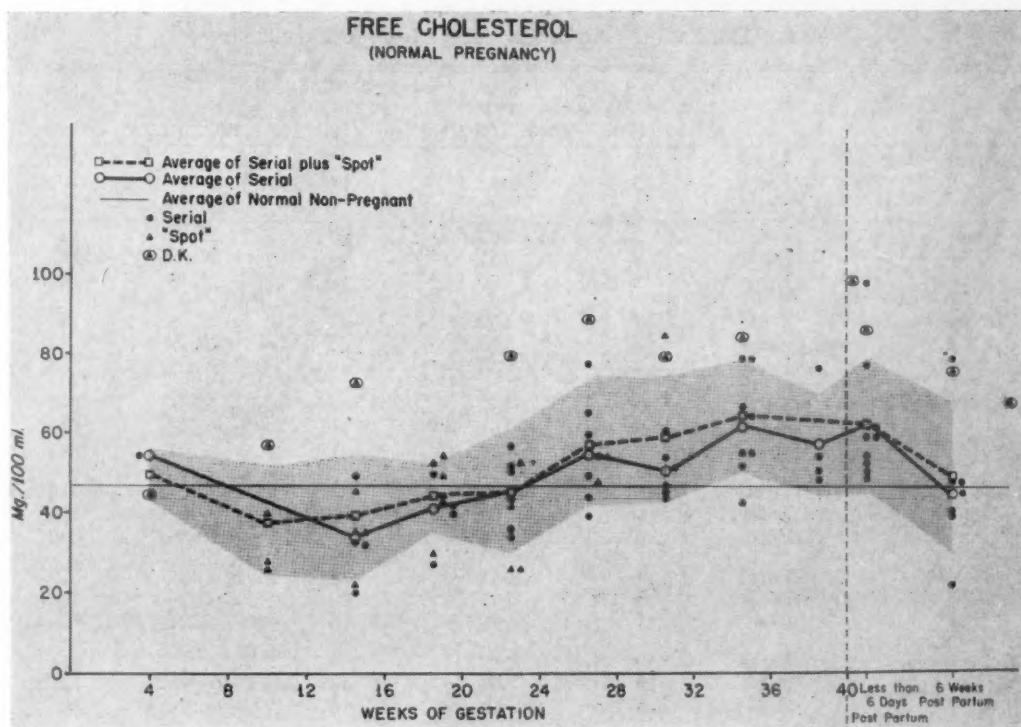


Fig. 5.—Serum free cholesterol determined during normal pregnancy. The solid line represents the mean of the group of patients upon whom serial determinations were made through pregnancy. The dotted line represents the average of the serial and "spot" patients. The standard deviation for the entire group is represented by the shaded area. "D. K." is a patient upon whom determinations were made serially from the fifth week of gestation through the late postpartum period.

**Ester Cholesterol.**—As with total cholesterol, statistically significant elevations in ester cholesterol do not begin until the twentieth week of pregnancy. The pattern of increased concentration thereafter follows the same general trend as that of total cholesterol, also reaching a maximum value of 149 per cent above the control group level as shown in Figs. 4 and 6 and in Table II. From this time until the sixth postpartum week, the values for ester cholesterol, like those for total cholesterol, decrease slowly, but at the sixth postpartum week have reached levels which are not statistically significantly different from those of the control group.

**Free Cholesterol.**—Free cholesterol differs from total and ester cholesterol in that values for free cholesterol remain within the same range as those of the control group up through the twenty-fourth week of pregnancy, as seen in

Figs. 5 and 6, and in Table II. It is not until the twenty-fifth to the twenty-eighth week of pregnancy that a statistically significant elevation occurs, with maximum values reached at the thirty-sixth week of pregnancy. During the last 4 weeks of pregnancy a rather sharp decrease occurs to levels which are not statistically significantly different from those of the control group. During the first few days after delivery, however, a significant rise in free cholesterol occurs with a gradual decline to normal control levels by the sixth to the seventh week post partum. As with ester cholesterol, the free cholesterol did not remain elevated to a statistically significant degree at 6 to 7 weeks postpartum. It is also noted that the standard deviations of free cholesterol are considerably larger during pregnancy than were seen in the control group, indicating the wide range of values during normal pregnancy.

TABLE II. SERUM CHOLESTEROLS IN NORMAL PREGNANCY

		NO. DETERMI- NATIONS	MEAN (MG./100 ML.)	STANDARD DEVIATION (MG./100 ML.)	PROBABILITY	% OF CONTROL
Control	Total	15	178	35		100
	Ester	15	131	36		100
	Free	15	46	5		100
0-8 weeks	Total	2	200	51	N. S.	112
	Ester	2	151	44	N. S.	115
	Free	2	50	6.3	N. S.	109
9-12 weeks	Total	4	152	41	N. S.	85
	Ester	4	115	27	N. S.	88
	Free	4	38	14	N. S.	83
13-16 weeks	Total	9	189	42	N. S.	106
	Ester	9	151	29	N. S.	115
	Free	9	39	16	N. S.	85
17-20 weeks	Total	10	207	31	<0.05	116
	Ester	10	163	29	<0.05	124
	Free	10	44	9	N. S.	96
21-24 weeks	Total	11	211	38	<0.05	119
	Ester	11	165	29	<0.02	126
	Free	11	46	16	N. S.	100
25-28 weeks	Total	10	239	56	<0.01	134
	Ester	10	180	44	<0.01	137
	Free	10	58	16	<0.02	126
29-32 weeks	Total	8	266	58	<0.001	149
	Ester	8	195	38	<0.001	149
	Free	8	59	16	<0.001	128
33-36 weeks	Total	9	257	44	<0.001	144
	Ester	9	193	35	<0.001	147
	Free	9	65	14	<0.001	141
37-40 weeks	Total	4	249	44	<0.01	140
	Ester	4	191	37	<0.02	146
	Free	4	58	13	N. S.	126
1-6 days post partum	Total	10	247	52	<0.001	139
	Ester	10	182	41	<0.01	139
	Free	10	63	17	<0.01	137
6-7 weeks post partum	Total	8	212	44	N. S.	119
	Ester	8	161	28	N. S.	123
	Free	8	50	19	N. S.	109

*Lipid Phosphorus.*—Data on lipid phosphorus are shown in Figs. 7 and 8 and in Table III. Since lipid phosphorus is a function of phospholipids, the



values for phospholipids are derived by a conversion factor of 25 from the lipid phosphorus values. The figures and tables also depict the values for phospholipids during normal pregnancy. While lipid phosphorus is the measured parameter, phospholipid probably represents the material transported in the blood. Differing from the trends noted in total and ester cholesterol, but similar to the trend noted with free cholesterol, an elevation of phospholipids did not reach a statistically significant level until after the twenty-fourth week of pregnancy. After the twenty-fourth week of pregnancy a sharp

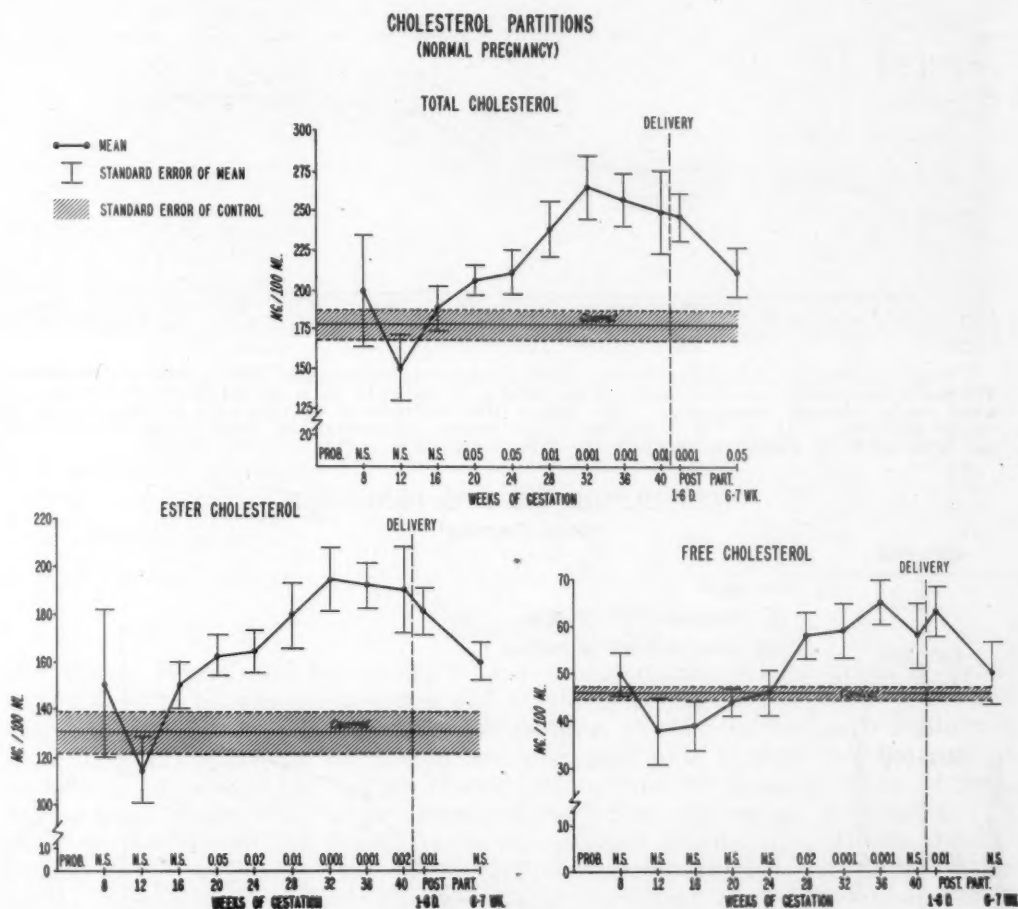


Fig. 6.—Cholesterol partitions, total, ester, and free cholesterol determined during normal pregnancy. All determinations are divided into groupings by lunar months ante partum, and into early and late postpartum groups. The solid curves represent the means of these groupings, and the vertical lines the standard error of each mean. The control group is composed of young, nonpregnant women. The shaded area represents the standard error of the control mean.

increase in the concentration of phospholipid occurred and persisted until term. This fraction differs from all other fractions thus far presented, except free cholesterol, in that a decline in the concentration of both free cholesterol and phospholipid did not occur during the first 6 postpartum days. The values increased steadily, reaching a peak of 140 per cent of the control value for phospholipid during the ninth lunar month of pregnancy. Immediately following delivery a slight increase in phospholipid occurred; this slight increase is similar to the pattern noted with free cholesterol immediately following delivery. It is also noted that, at the sixth to the seventh week post

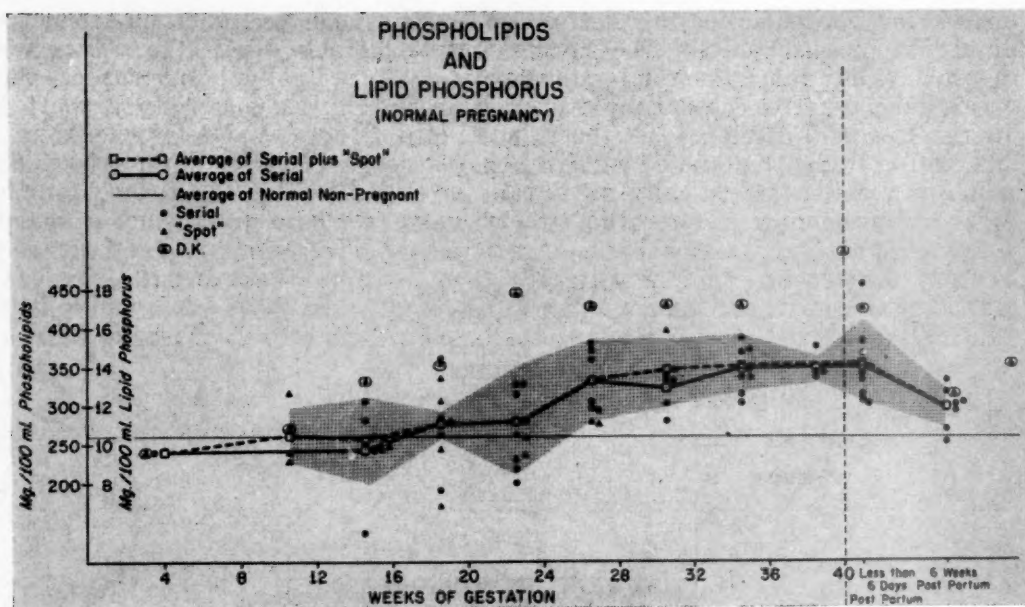


Fig. 7.—Serum phospholipids and lipid phosphorus determined during normal pregnancy. The solid line represents the mean of the group of patients upon whom serial determinations were made through pregnancy. The dotted line represents the average of the serial and "spot" patients. "D. K." is a patient upon whom determinations were made serially from the fifth week of gestation through the late postpartum period.

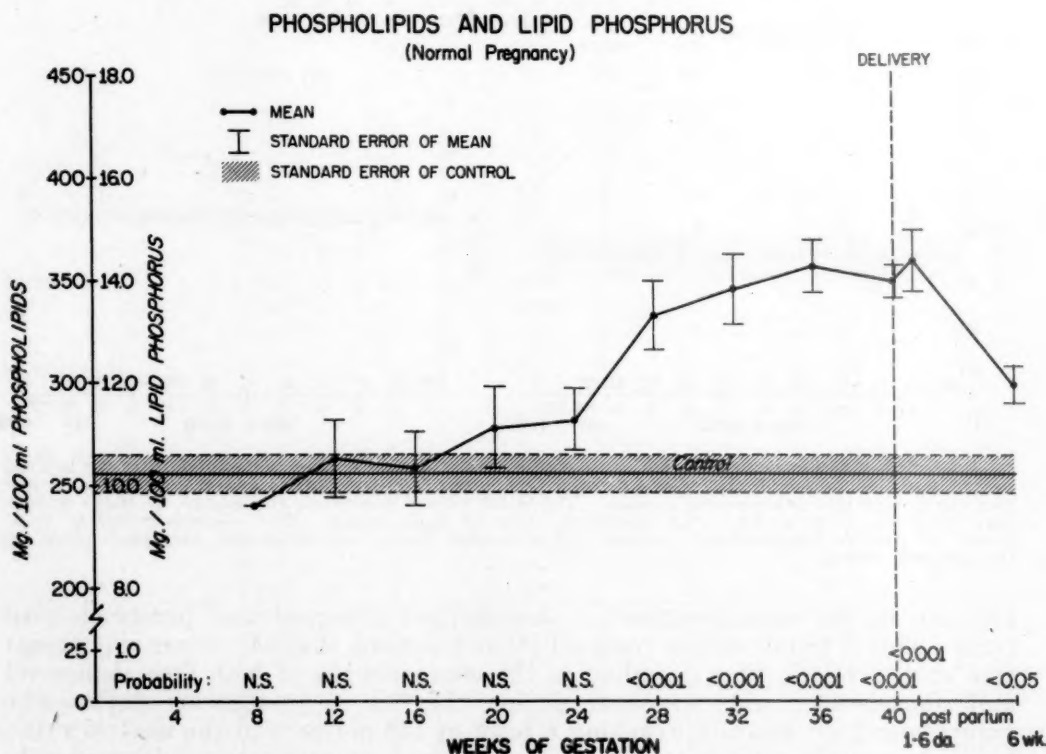


Fig. 8.—Serum phospholipids and lipid phosphorus determined during normal pregnancy. All determinations are divided into groupings by lunar months ante partum, and into early and late postpartum groups. The solid curve represents the mean of these groupings, and the vertical lines the standard error of each mean. The control group is composed of young, nonpregnant women. The shaded area represents the standard error of the control mean.

partum, the concentration of phospholipid was still well above that found in the control group or during early pregnancy. The value at this time was significantly different from the control value.

TABLE III. SERUM LIPID PHOSPHORUS AND PHOSPHOLIPID IN NORMAL PREGNANCY

		NO. DETERMI- NATIONS	MEAN (MG./100 ML.)	STANDARD DEVIATION (MG./100 ML.)	PROBABILITY	% OF CONTROL
Control	Lipid phosphorus	15	10.1	1.9		100
	Phospholipids	15	256	36		100
0-8 weeks	Lipid phosphorus	2	9.6	0	N. S.	95
	Phospholipids	2	240	0	N. S.	94
9-12 weeks	Lipid phosphorus	4	10.5	1.5	N. S.	104
	Phospholipids	4	263	37	N. S.	103
13-16 weeks	Lipid phosphorus	9	10.3	2.2	N. S.	102
	Phospholipids	9	258	55	N. S.	101
17-20 weeks	Lipid phosphorus	10	11.1	0.8	N. S.	110
	Phospholipids	10	278	64	N. S.	109
21-24 weeks	Lipid phosphorus	11	11.3	2.8	N. S.	112
	Phospholipids	11	282	49	N. S.	110
25-28 weeks	Lipid phosphorus	10	13.3	2.1	<0.01	132
	Phospholipids	10	333	53	<0.001	130
29-32 weeks	Lipid phosphorus	8	13.8	1.9	<0.001	137
	Phospholipids	8	346	48	<0.001	135
33-36 weeks	Lipid phosphorus	9	14.3	1.5	<0.001	141
	Phospholipids	9	357	39	<0.001	139
37-40 weeks	Lipid phosphorus	4	14.0	0.7	<0.01	139
	Phospholipids	4	350	16	<0.001	137
1-6 days post partum	Lipid phosphorus	10	14.4	2.0	<0.001	143
	Phospholipids	10	360	48	<0.001	141
6-7 weeks post partum	Lipid phosphorus	8	11.9	1.0	<0.02	118
	Phospholipids	8	299	26	<0.05	117

### Comment

While Peters and his group<sup>16</sup> have reported that serum lipids in pregnancy tend to lie somewhat below the accepted average for a group of normal nonpregnant individuals, no statistical support of this contention is contained in their data. In early pregnancy we have been able to show on the basis of our data, supported by statistical evaluation, that the concentration of total lipids, total cholesterol, ester cholesterol, and free cholesterol is variable. In each of the cholesterol fractions in the various groups of patients studied during early pregnancy, the values, for the most part, fall within the range of the normal nonpregnant patient. With the exception of free cholesterol, there is little tendency for the values to fall below the normal nonpregnancy values during early pregnancy. Once the rise in lipids is initiated, the increase is progressive as pregnancy advances. The rise in these fractions has been variously stated by observers to be related to increased concentration of various steroids known to occur during pregnancy. Work in our laboratory has not shown any correlation between the rise in serum lipids and the concentration of total urinary 17-hydroxycorticosteroids.

Gardner and Gainsborough<sup>17</sup> found indefinite changes in total cholesterol; they found free cholesterol to increase relatively more than did ester cholesterol. This observation is in conflict with our data. Boyd<sup>5</sup> found plasma neutral fat and phospholipids to increase markedly during pregnancy but free and ester cholesterol did not differ dramatically from nonpregnancy levels, although there was a slight increase in both of these fractions. He believed the changes in phospholipids and cholesterol to be secondary to an increase



in neutral fats; he felt that neutral fats rose during the first trimester while phospholipids and cholesterol rose coincidentally from the second trimester to term. Tyler and Underhill<sup>18</sup> found total cholesterol, cholesterol ester, and lecithins to rise during pregnancy but they used whole blood in performing their determinations. Dieckmann and Wegner,<sup>6</sup> using Bloor's method, found total cholesterol to increase to 23 per cent above the first trimester levels and to decrease 27 per cent at the eighth postpartum week from the values noted at term. This rise noted by Dieckmann is considerably lower than our findings of a 54 per cent increase in the third trimester values above the first trimester values for total cholesterol and a 23 per cent decrease in the values 6 to 7 weeks post partum for total cholesterol as compared to the third trimester values.

Watson,<sup>19</sup> in one of the most recent publications dealing with serum lipids in pregnancy, performed a serial study throughout gestation and the puerperium. While his methods differed slightly from ours, he found total cholesterol to increase progressively through the twenty-ninth week, at which time it remained elevated through parturition and the early puerperium. He also determined beta:alpha lipoprotein ratios and found the beta lipoprotein to increase relatively to the alpha lipoprotein. This is in agreement with our findings. Oliver and Boyd<sup>20</sup> found total cholesterol and the cholesterol fractions to increase to levels similar to those found by us. They noted a 25 per cent increase in phospholipids between the ninth and thirty-third weeks of pregnancy. The increase in phospholipids noted in our patients was 44 per cent between the eighth and thirty-second weeks of pregnancy.

Thus, using newer techniques and similar type samples, there seems to be general agreement by most workers that during normal pregnancy an increase occurs in total lipids, total, ester, and free cholesterol, phospholipids, and the beta:alpha lipoprotein ratios.<sup>21-26</sup>

Even though the findings during normal pregnancy may seem obvious, the factors responsible for these changes are, however, not quite so clear-cut. Recently considerable investigation has been focused on both the endocrine regulation of fat metabolism<sup>27</sup> and the hormone changes during pregnancy.<sup>28, 29</sup> The principal areas of interest and reporting have been concerned with the pituitary, thyroid effects, the adrenal cortex, and the ovarian steroids.

The hypertrophy of the anterior pituitary gland during normal pregnancy is well known. That the "pregnancy cells" are actively secreting is concurred in as well.<sup>30</sup> Hyperlipemia and hypercholesterolemia frequently accompany acromegaly. Such increases in these lipids might, however, more probably be related to diabetes or to other disorders frequently accompanying anterior pituitary hyperfunction rather than to pituitary changes alone.<sup>31</sup> The nature of the secretions of the "pregnancy cells" is as yet unknown but it is quite possible that they could well differ from the secretions of the normal pituitary in the nonpregnant individual. Thus, any direct effect of the pituitary on lipid metabolism during normal pregnancy must remain conjectural.

Extensive studies have been carried out to determine the exact role of the thyroid in lipid metabolism during pregnancy. The results of these investigations do not offer absolute conclusions. Numerous workers have shown that the protein-bound iodine and serum precipitable iodine are elevated<sup>32, 33, 34</sup> as early as the second month of pregnancy. These levels have been found to reach values as high as those seen in individuals with overt hyperthyroidism.<sup>34</sup> Pregnancy seems, at least in some cases, however, partially to eclipse symptoms of hyperthyroidism. Thus, although thyroid hormone has been found to depress all of the serum lipid partitions,<sup>35, 36</sup> it does seem that during pregnancy the tissues become more refractory to the effects of thyroxin.

Estrogens were implicated as influencing serum lipids, particularly phospholipids, total cholesterol, and alpha:beta lipoprotein, as a result of investigation demonstrating sex differences during the reproductive years.<sup>37-41</sup> In the more recent investigations the fact that estrogens do indeed affect lipid partitions in plasma has been confirmed. Adlersberg<sup>27</sup> feels that estrogens tend to increase the proportion of lipid in the form of alpha lipoprotein. Eilert<sup>42</sup> found that estrogen administered to women evoked an increase in the plasma total lipids. Russ and associates<sup>43</sup> found that the administration of estrogen lowered the beta lipoprotein but raised the alpha lipoprotein. Furman and co-workers<sup>44</sup> found an increase in alpha lipoprotein following the administration of estrogen but noted a rather inconsistent response of beta lipoprotein. It seems that the consensus supports the contention that estrogen increases the alpha lipoprotein fraction whereas the findings during pregnancy, including our own, tend to confirm an increase in beta lipoprotein, in addition to the changes already noted.

The adrenal cortex has long been thought to influence plasma lipid levels and the extensive investigation has confirmed this thesis. Adlersberg and his associates<sup>45, 46</sup> showed that the administration of cortisone produces an increase in total serum cholesterol and phospholipids but tends to effect a reduction in neutral fat. Gemzell<sup>47</sup> reported a fourfold increase in plasma 17-hydroxycorticosteroids during normal pregnancy and other studies have substantiated increased adrenocortical activity in pregnancy. Just how many of the changes in serum lipids in pregnancy are due to the adrenal cortex, however, is still debatable and must await further study.

In 1952, Chino<sup>48</sup> found that immunization of rabbits with egg albumin or sheep corpuscles was followed by substantial elevation of total, ester, and free cholesterol, phospholipids, neutral fat, and total lipids. It is interesting to speculate whether such a factor might operate during even normal pregnancy, inasmuch as the mother is sensitized to various fetal antigenic substances crossing the placenta or entering the maternal circulation through disruptions in the continuity of small villi. The lack of absolute integrity between fetal and maternal circulation has been pointed out by Hedenstedt and Naeslund,<sup>49</sup> Mengert and his associates,<sup>50</sup> and Chown.<sup>51</sup> It thus seems that the chances for maternal immunization reactions would be great indeed.

### Summary and Conclusions

1. Serial and spot studies of the various lipid fractions during normal pregnancy are presented. The partitions studied include serum total lipids, total cholesterol, ester cholesterol, free cholesterol, lipid phosphorus and phospholipids, and lipoprotein distribution.

2. During early pregnancy the values for total cholesterol, ester cholesterol, free cholesterol, lipid phosphorus and phospholipids, as well as total lipids, do not differ significantly from those for normal nonpregnant controls. Even though the trend of free cholesterol shows a decrease during early pregnancy, the differences are not statistically significant when compared with control values.

3. All values are increased as pregnancy approaches term, with a return to normal for most fractions by the sixth postpartum week; total lipids and lipoproteins are the principal exceptions.

4. While estrogen reportedly effects an increase in alpha lipoprotein, pregnancy produces an increase in beta lipoprotein. The changes in the

blood lipids during pregnancy, on the basis of our study, cannot be accounted for by the increase in estrogen alone or by an increase in adrenal steroids alone.

5. For a better comprehension of the interrelationships of obstetric endocrinology and lipid metabolism, not only must improvement be made in methods for determining the various steroids in plasma and in urine but also an increased knowledge of lipid metabolism and its regulation must be forthcoming before such interdependent relationships can be worked out.

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### Discussion

DR. ALLAN C. BARNES, Cleveland, Ohio.—The cynic has been heard to say that the shifting trends in our basic studies on pregnancy are less influenced by our interests in the patient's physiology than by new research equipment as it is developed. In support of this they cite the rise in reports dealing with electrolyte and water metabolism which followed the improvement and standardization of the flame photometer. And on this same basis they suggest that our increasing interest in the area Dr. de Alvarez turns our attention toward today is dictated chiefly by the laboratory techniques for lipid identification, particularly its fractionation and measurement by electrophoresis.

This, of course, is a perfectly true observation; the development of the theory of cellular pathology had to await the perfection of the microscope. Or, putting it the other way around, there is an obligation resting on the conscientious investigator to seize each refinement and improvement in methodology and to apply it to the perplexing problems in our field. Dr. de Alvarez' presentation offers us such a conscientious application of the newer (and, we hope, more accurate) methods for lipid identification to the physiology of lipid metabolism in pregnancy and the puerperium. And it would be safe to venture the prediction that we will see an increase in the number of reports in this area. Thus, while there were at the beginning of 1958 only two papers in the combined American and Canadian literature dealing with lipoprotein fractions at term, particularly as related to fetal levels, there are, at the present time, many institutions carefully investigating these changes.

Dr. de Alvarez' findings with respect to the major fractions studied would indicate that they all rise markedly in the last trimester. These rises are not completely consistent in time of appearance, nor are they necessarily proportionate. Their etiology cannot be determined at present (although he summarizes the leading theories for us) nor is their significance completely understood.

Our own interest has been in a comparative analysis of the lipoprotein fractions in pregnancy and the curious relationship between the beta and alpha fractions mentioned by Dr. de Alvarez. Using the Wahl modification of the Durrum electrophoresis apparatus, and the oil red O stain which Dr. de Alvarez employed, Dr. John Buckingham working in our clinic has run determinations of these fractions on some 37 patients, both serially and by the spot-check method, including nonpregnant controls, normal and toxemic pregnant women, together with studies of the newborn in some cases.

In general these studies confirm the rise in the percentage of beta lipoprotein as pregnancy advances which has been indicated by others. But, more interesting to us, and possibly more significant, is the fact that the pre-eclamptic patients show the least variation in range with respect to the percentage of beta lipoprotein found, and, in all cases studied to date, the sera from pre-eclamptic patients have consistently shown the highest percentage of beta lipoprotein of all the groups studied.

As Dr. de Alvarez indicates, it is still premature to draw extensive conclusions as to the various possible mechanisms to explain these changes. These findings do not permit us, however, to dismiss lightly the sensitivity response theory for the toxemias of pregnancy. After indicating that the estrogen changes or the increase in adrenal corticoids does not provide a satisfactory explanation for the changes he has reported, Dr. de Alvarez contents himself with pointing out that the chance for such maternal immunization reactions would be great.

In an area of increasing interest, Dr. de Alvarez has given us today a thoughtful evaluation of the past and the possible future of such studies of serum lipids, together with an



excellent presentation of his own baseline studies. This must of necessity be a preliminary report. Armed with the newer techniques for the study of these components, we must continue to explore such changes in lipid metabolism.

DR. W. NORMAN THORNTON, JR., Charlottesville, Va.—Dr. de Alvarez' study is particularly apropos in view of the many observations suggesting that altered fat metabolism has more than a casual relationship to degenerative vascular disease. The magnitude of the lipemia incident to pregnancy is not fully displayed by Dr. de Alvarez' figures since they do not take into consideration the increase in plasma volume known to be associated with gestation.

Since coronary thrombosis is relatively rare during the reproductive life of women, the marked lipemia incident to gestation could be interpreted as evidence that increased circulating fat does not constitute a primary etiological factor in the deposition of atheromatous plaques. The question remains, however, as to whether the total quantity of circulating lipids constitutes the significant factor, or the concentration of these fats, or the relative quantities of the various lipid fractions which may be present. It is, moreover, possible that the duration of the lipemia may represent the determining factor.

It is of interest to note that patients with nephrotic and liver disease are prone to have vascular complications, while those with biliary cirrhosis are not, despite an abnormal elevation of the plasma cholesterol in both groups. Gertler and Oppenheimer (*Geriatrics* 9: 157, 1954) have suggested that the significant factor is the ratio of the concentration of cholesterol to that of the phospholipids in the serum, since phospholipids may hold the hydrophobic cholesterol in suspension. As evidence of this one finds that a high C/P ratio may be associated with a milky serum, aggregates of lipid particles, and the deposition of cholesterol in the tissues.

In view of these considerations, it is interesting to compare the C/P ratio for Dr. de Alvarez' series with values for males of a comparable age span obtained from the data of Gertler and Garn (*Science* 112: 14, 1950). As noted in the tabulation, the C/P ratio for pregnant women is essentially the same as for the control group of women, and within the range of the ratio for normal males.

	CHOLESTEROL (MG. %)	PHOSPHOLIPID (MG. %)	C/P RATIO
Normal males	224.4	299.3	0.75
Coronary thrombosis	286.5	316.4	0.89
Nonpregnant women	178.0	256.0	0.70
Pregnant women (term)	249.0	350.0	0.71

We anxiously await Dr. de Alvarez' future studies pertaining to the lipid pattern in toxic gestation, particularly in view of the observations of Zeek and Assali (*Am. J. Clin. Path.* 20: 1099, 1950) on atherosclerotic changes in the uteroplacental vessels incident to toxemia. Certainly the problem is complex. For example, one is prone to question whether an elevation in lipid concentration in toxemia might not appear coincidentally with a contraction of the plasma volume, and thus be in association with a true pathologic disturbance of lipid metabolism.

It appears that two experiments are needed to clarify the role of the serum lipids in the etiology of the toxemias of pregnancy. In one, a series of patients would be given a sufficiently increased intake of fat as to result in an elevated serum cholesterol concentration. A second group would be given sitosterol or nicotinic acid which are said to lower the blood cholesterol level. The determination of the various lipid fractions and ratios, plus changes in the incidence of pre-eclampsia and eclampsia in these groups as compared with untreated patients might clarify some of the problems.

Dr. de Alvarez has commented on several possible factors which may play a role in the production of the lipemia of normal pregnancy. Whatever the mechanisms involved, it is of interest that the serum lipid levels begin their rise coincidentally with the onset of the

period of maximal weight accumulation in the products of conception. It would be of considerable interest to determine lipid concentrations in blood samples taken from the placental pool by means of transabdominal aspiration for comparison with those present in the blood of the umbilical arteries and vein of the newborn.

In closing, I would like to ask Dr. de Alvarez two questions pertaining to the persistence of the lipemia after delivery:

1. Was it correlated with blood loss at delivery, since hemorrhage is known to be followed by an elevation of serum lipids?
2. Was it correlated with lactation?

DR. DE ALVAREZ (Closing).—What Dr. Barnes stated about more accurate identification of lipids is quite true. The methodology of study of the lipid fractions, not only of the major classes but also of the electrophoretic patterns of the lipoprotein fractions, is constantly undergoing change, so that even in our own laboratory it may be necessary for us to report again 5 years hence on the same subject. The increases in each fraction of lipids do not occur concurrently at the same duration of pregnancy. Why these happen thus is not clear, but the change may be related to the serum protein concentration, which also changes when studied serially in the normal pregnant patient. Even though we determine a relationship, we have not yet determined whether the relationship in the changes in the serum proteins is proportionate to the lipoprotein changes.

Dr. Barnes stated that in his experience lipid metabolism in the pre-eclamptic patient shows the least variation. While we are not prepared to discuss fully our results in the pre-eclamptic patient, we can say that statistical analysis of our data reveals no statistically significant difference in pre-eclampsia and eclampsia from normal pregnancy. I think that some of the differences attributed to toxemia really represent comparisons with nonpregnant patients, rather than with data obtained from the normal pregnant patient. Of course, most of these studies in patients with pre-eclampsia-eclampsia are done close to term or in the immediate puerperium because the toxemic process occurs at that time; thus the values would be markedly different from those of the nonpregnant patient or even from those of early normal pregnancy, but not different from the values for the near-term normally pregnant patient.

Dr. Thornton has raised the point as to whether plasma volume has anything to do with the concentrations of lipid. As pregnancy advances, the concentration of lipid increases. The level of plasma volume in our group of normal pregnant patients rises earlier than the often stated twenty-eighth to thirty-second week of pregnancy, so that we have noted no specific relationship except that both plasma volume and percentage of lipid concentration seem to increase relatively early in normal pregnancy. As a matter of fact, in some instances, plasma volume has reached a higher level at the third month than at the sixth to the seventh month of pregnancy.

The persistent lipemia in the postpartum patient in our series was not related to blood loss at delivery nor was it related to lactation. Even though the findings in the group from the first to the sixth postpartum day may be related to the period at which breast congestion occurs, the drop in lipids was not nearly so pronounced in the first 5 to 6 postpartum days as it was after this period. In one patient followed for 6 months after delivery, lipid values had not yet reached the control levels by the fifth month post partum but did return to normal nonpregnancy levels at the sixth month. A prolonged period of time seems necessary after a pregnancy for the alterations in lipid levels which occur as a result of pregnancy to return to normal.

## PREGNANCY SUBSEQUENT TO LIGATION OF THE INFERIOR VENA CAVA AND OVARIAN VESSELS\*†

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LIGATION of the inferior vena cava and ovarian veins in the human interrupts the normal venous return from the pelvis and lower extremities. That pregnancy can occur subsequently and follow a normal course has been reported by us in previous communications.<sup>1, 2</sup> The description of 15 such pregnancies was presented before this organization in 1951. We are now prepared to give our observations of 47 instances of pregnancy subsequent to ligation of the inferior vena cava and ovarian vessels.

TABLE I. RECORD OF FOLLOW-UP OF PATIENTS

YEAR OF LIGATION	YEARS SINCE OPERATION	NO. OF PATIENTS
1957	1	0
1956	2	0
1955	3	1
1954	4	1
1953	5	0
1952	6	1
1951	7	2
1950	8	3
1949	9	4
1948	10	3
1947	11	3
1946	12	0
1945	13	2
1944	14	2
1943	15	0
1942	16	1

### Material

Since 1941, members of our department have ligated the inferior vena cava and ovarian veins of 140 women. The great majority of them were done on the Tulane Service at Charity Hospital of Louisiana in New Orleans. Twenty-three of these women are known to have become pregnant subsequent to ligation. Sixteen of these 23 patients were registered in our clinics and 7

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were managed by private physicians during their antenatal, intrapartal, and postpartal courses. Review of their records disclosed 47 instances of pregnancy subsequent to ligation of the inferior vena cava and ovarian vessels. The first instance of postligation pregnancy in this group occurred in 1942. One woman is now pregnant and due to be delivered in September, 1958. Thus over a 16 year period and at varying intervals subsequent to ligation these women have provided us an opportunity to evaluate the immediate and late effects of the procedure on their childbearing functions (Table I).

### Interval From Ligation to Conception

The case histories indicate that 22 of these patients conceived within 48 months of ligation. One patient did not conceive until 84 months after operation. The earliest conception was within 4 months. The 23 initial pregnancies subsequent to ligation occurred as illustrated (Fig. 1). We emphasize that these 23 women had had severe infection of the pelvic vessels and uterus, and that medical regimen had failed to overcome the infections. Ligation of the inferior vena cava and ovarian veins was done as a lifesaving procedure. It is interesting that 10 of these initial 23 postinfection, postligation pregnancies produced live babies and that there was no correlation of these favorable results with the interval from ligation to conception (Fig. 2). It is also of note that all 13 of the abortions occurred in the group of clinic patients and that 8 of these same women later had viable births.

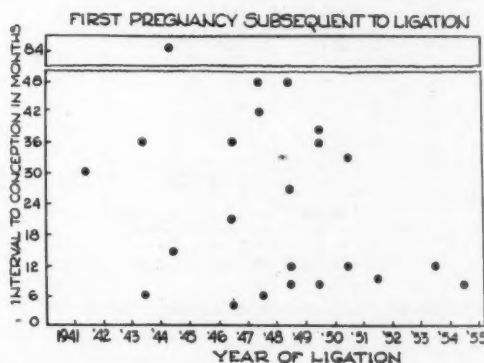


Fig. 1.—Interval from ligation to first postligation pregnancy.

### Viable Pregnancies

Pregnancies that were carried successfully beyond 28 weeks were considered viable. These 23 women had 47 pregnancies after ligation of the inferior vena cava and ovarian veins. Thirty of these pregnancies extended beyond 28 weeks. Of these 30 pregnancies, 22 progressed to term, 7 terminated prematurely, and one woman at the time of this writing is 34 weeks pregnant. It is interesting that all 7 of the women under private care carried their pregnancies to term. They accounted for 11 of the term births. The 16 women in the clinic category had the remaining 19 viable pregnancies and all of the 17 postligation abortions (Fig. 3). We do not believe that the difference in results was due to the care available to the clinic patients but reflects rather the attitude of the patients who attend our free clinics.

### Antenatal Care

The patients under the care of private physicians and our clinic patients received antenatal care that was no different from the care received by



pregnant women who had not had ligation of the inferior vena cava and ovarian vessels. We had detailed reports from the physicians in charge of 4 of the private patients, but did not have access to any of the private records for personal review. We were able to review all records of the 16 clinic patients. In several instances, the histories of these 16 patients included the accurate course of their pregnancies prior to ligation.

We were impressed that the clinic patients who had had ligation received no more attention than our other clinic patients. In fact in their antenatal period they were checked by medical students, nurses, interns, or residents. They neglected themselves in several instances. Some did not report for care until they had had abortions or until their pregnancies were in the last trimester, or even until they were already in labor. When we had the opportunity, we requested them to report to a special clinic so that we could make more accurate notations as to their status or study various factors of interest to us in women who had had inferior vena cava and ovarian vein ligation. These patients were on no special regimen of diet, drugs, exercises, or restriction of activity, nor were they instructed to wear special shoes, stockings, clothing, or

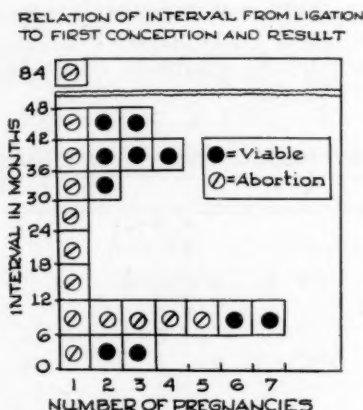


Fig. 2.—Interval from ligation to first postligation pregnancy in 23 patients and result.

supports of any kind. Some of the symptoms and signs particularly sought were claudication, varices of the leg veins, vulvar veins, vaginal veins, hemorrhoids, dilated abdominal veins, or significant edema of the legs or vulva. Our observations disclosed no significant change from the normal. There were no instances of vulvar or vaginal varices. One patient who had varices of the lower extremities prior to ligation continued to have the same problem and one other patient had a postphlebitis syndrome. No problem of hemorrhoidal veins was described or recorded antenatally or during labor. There were a few recordings of transient 1 plus edema but in no instance was there significant, persistent, or progressive edema of the lower extremities. All of these patients continued their former activities as domestics or housewives or both during and after their pregnancies except when specific problems of pregnancy per se necessitated hospitalization. These complications are discussed below. Figs. 4, A and B, compares the vulva of a pregnant woman of 32 weeks' gestation who had had a vena cava ligation in 1944 and that of a control of equal age and parity. The patient who had the ligation had had 5 pregnancies prior to ligation and is now in her sixth postligation pregnancy. The control is a patient of equal age, parity, and gestation who did not have a history of vascular disease or operations. We are unable to show any difference in appearance, edema, or varices of the vulva or vagina. Figs. 5, 6, and 7 are infrared

photographs of these same 2 women. We see a slight increase in the prominence of the superficial leg veins of the patient who had had ligation but otherwise we cannot show any significant features in this comparison.

### Antepartal Complications

Complications of the viable pregnancies were few (Table II). Varices of the lower extremities were marked in one patient. She had the same problem prior to ligation. It is of interest that her 2 term postligation pregnancies showed no progressive increase in the severity of the varices.

A postphlebitis syndrome occurred in one patient following ligation. She had no term pregnancies after ligation; therefore, we could not observe the effects of pregnancy on her legs. Her one postligation pregnancy ended in an abortion at 10 weeks. There was no recording of any exacerbation at the time of abortion.

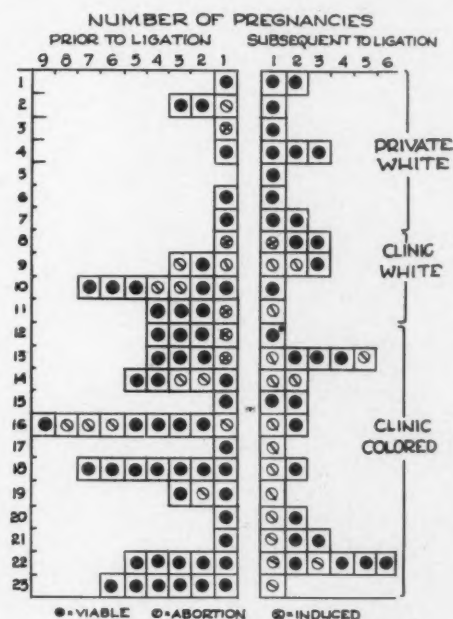


Fig. 3.—Comparison of pregnancies and results thereof in 23 patients. *Left*, Prior to ligation *Right*, Subsequent to ligation.

Pre-eclampsia occurred in one of the patients under private care. She had had suppurative pelvic thrombophlebitis with pulmonary infarction after a cesarean section for severe pre-eclampsia in 1950. After ligation, she had two pregnancies, the first in 1955 with pre-eclampsia and repeat cesarean section. A live baby was obtained. The second postligation pregnancy again was characterized by pre-eclampsia, intrauterine death of the baby at 38 weeks' gestation, and cesarean section hysterectomy. Following this last pregnancy and operation she has developed recurrent phlebitis of the left leg.

TABLE II. ANTENATAL COMPLICATIONS IN VIABLE PREGNANCIES

No complications	22
Bleeding	4
Pre-eclampsia	2
Urinary tract infection	1
Varicose veins of leg	1
Total	30

One of our postligation patients developed urinary symptoms and pyuria in the second trimester of pregnancy. She was hospitalized and treated and she recovered uneventfully. The pregnancy then proceeded uneventfully to term without recurrence of the urinary problem.

Four pregnancies were complicated by bleeding that led to special procedures. One of the private patients had spotting when 10 weeks pregnant. Her private physician did a laparotomy for ectocyesis and found a normal intrauterine pregnancy. The hemoperitoneum was from a ruptured corpus luteum. The pregnancy proceeded to term uneventfully. One clinic patient had moderate,

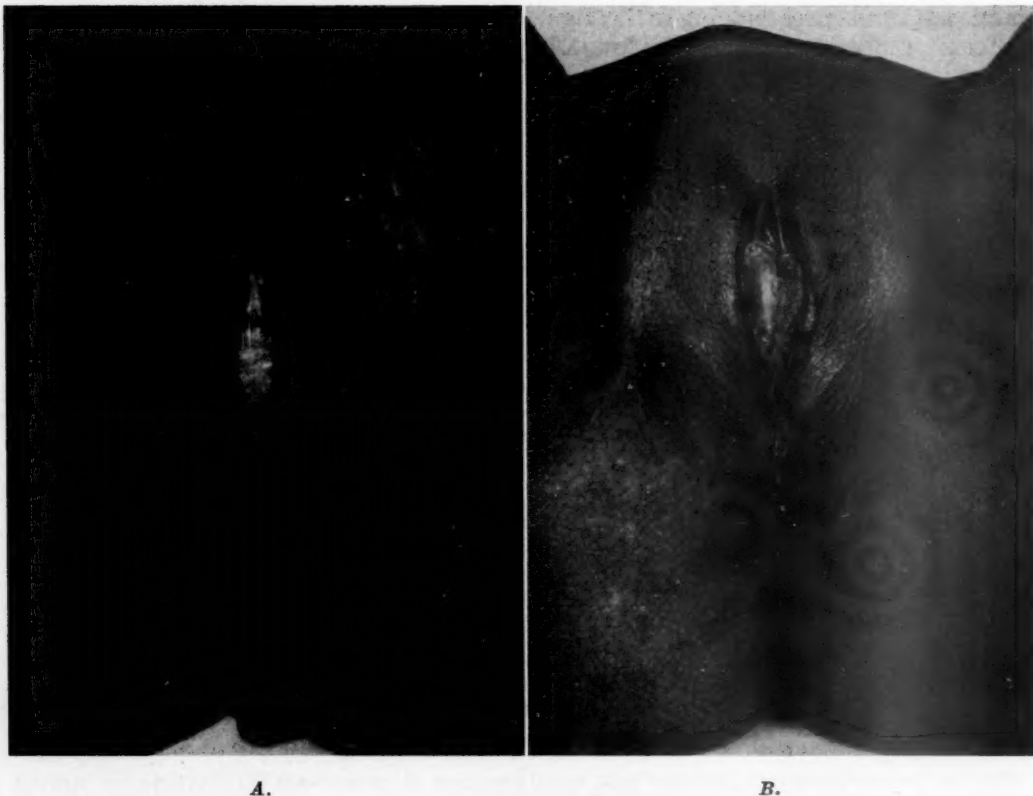


Fig. 4.—A, Photograph of vulva in pregnancy subsequent to ligation. B, Photograph of normal vulva compared to that of patient who had ligation. Both patients now 32 weeks pregnant and of the same parity.

painless bleeding at term. This was her third postligation term pregnancy. Cesarean section was performed and revealed bleeding from a marginal sinus rupture in a circumvallate placenta. The baby survived. The mother had 3 days of puerperal morbidity attributed to endometritis but was discharged on the tenth postsection day. At the time of cesarean section, no unusual engorgement of the abdominal wall, the uterus, or parametria was encountered, nor was there any problem in the degree of bleeding from the abdominal or uterine incisions. The surgeon's operative note recorded that he encountered nothing unusual in this operation as compared to a cesarean section in a woman who had not had previous inferior vena cava ligation.

The other 2 instances of bleeding occurred in one other patient. She has had 5 pregnancies subsequent to ligation. In the first, that proceeded to viability, bleeding began in the third trimester. She was hospitalized for a

month. During this time she continued to bleed. Repeated transfusions were given. Delivery occurred at 32 weeks with a viable 2 pound infant who survived. The next pregnancy resulted in the same complication, again with hospitalization, transfusions, and delivery at 36 weeks of a viable, surviving infant. The next pregnancy terminated at 34 weeks without antenatal bleeding. On this occasion twins, weighing 4 pounds, 4 ounces, and 4 pounds, 11 ounces, were delivered. Both babies survived. It is interesting that this patient had one of the most severe instances of suppurative pelvic thrombophlebitis necessitating ligation in our entire series. At the time of operation in 1949, the



A.

B.

Fig. 5.—A, Infrared photograph of abdominal veins of patient who had ligation, now 32 weeks pregnant. B, Infrared photograph of abdominal veins of patient who had not had previous surgery or vascular disease, now 32 weeks pregnant.

thrombophlebitis of the right adnexa and vena cava was so extensive that we resected the right ovarian veins, ovary, and fallopian tube and a thrombosed segment of the inferior vena cava. Details of this patient's case history have been reported.<sup>3</sup>

### Labor, Delivery, and Puerperium

Twenty-nine pregnancies were delivered and one patient is now pregnant and due to be delivered in September, 1958. Twenty-four of these deliveries were vaginal. There were 5 cesarean sections. Labor and delivery in the private patients were not remarkable except that 4 of the 5 cesarean sections were in this group. We had detailed information on delivery only in the private patient who had the 2 repeat cesarean sections. In our clinic group, the labor records were more detailed. In all but one instance, the clinic



patients' labor was under the observation and guidance of medical students, interns, or, in a few instances, residents. The exception was one woman who was delivered in a rural house, unattended. Only the patients described above under the heading of complications had any difficulties in labor and delivery. These were the instances of antenatal bleeding and the case of pre-eclampsia in a private patient. The duration of labor was in some instances as short as 45 minutes and in one patient 14 hours. The conduct of labor was the same as for any other patient.

We used no special techniques, no prophylactic antibiotics or anticoagulants, and we did not insist on special anesthesia. In fact, several types of anesthesia were employed in the 29 deliveries. Some patients had no anesthesia, others local, spinal, or general. The type of anesthesia was determined entirely by the obstetrical status and not by the patient's history of

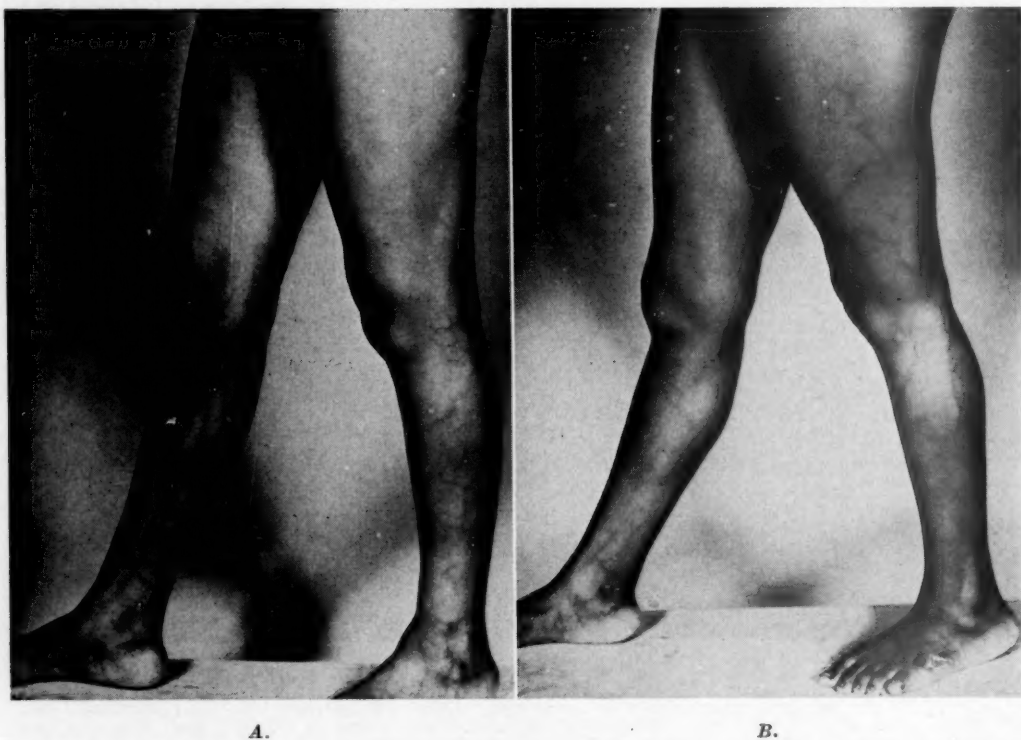


Fig. 6.—A, Infrared photograph of leg veins, lateral view, of patient who had ligation, now 32 weeks pregnant. B, Infrared photograph of leg veins, lateral view, of patient who had not had previous surgery or vascular disease, now 32 weeks pregnant.

inferior vena cava ligation. The same obstetrical criteria determined the use of forceps and/or episiotomy. In no instance was delivery difficult. The third stage was notable in that in 2 instances manual removal of the placenta was necessary. In one of these patients, blood transfusion was necessary. The other bleeding problems have been described previously.

There were 5 cesarean sections. Two of the private patients had had cesarean section prior to ligation. Neither of these babies survived. After ligation, one of these women had 2 repeat cesarean sections with viable babies that survived. The other patient was described as having pre-eclampsia with all her pregnancies, the one before ligation as well as the 2 pregnancies subsequently. Only one of her babies lived and that one was born by her first post-ligation repeat cesarean section. The second was stillborn at the time of her

second postligation repeat cesarean section at 38 weeks' gestation. Her physician elected at that time to do a cesarean section hysterectomy. It is of note that although we had no description of the placenta of her preligation pregnancy, both placentas of her postligation pregnancies were described as being very small and fibrotic.

The fifth cesarean section was done for painless bleeding at term. The findings were circumvallate placenta and ruptured marginal sinus. This has been discussed previously (Table III).

The puerperium was complicated in 4 instances, 3 from bleeding, already discussed, and once by endometritis in the postligation cesarean section discussed above. The late puerperal examinations at the sixth postpartal week in 28 instances were normal. In one patient, the one who had the cesarean section hysterectomy, intermittent phlebitis of the left leg has required attention.



A.

B.

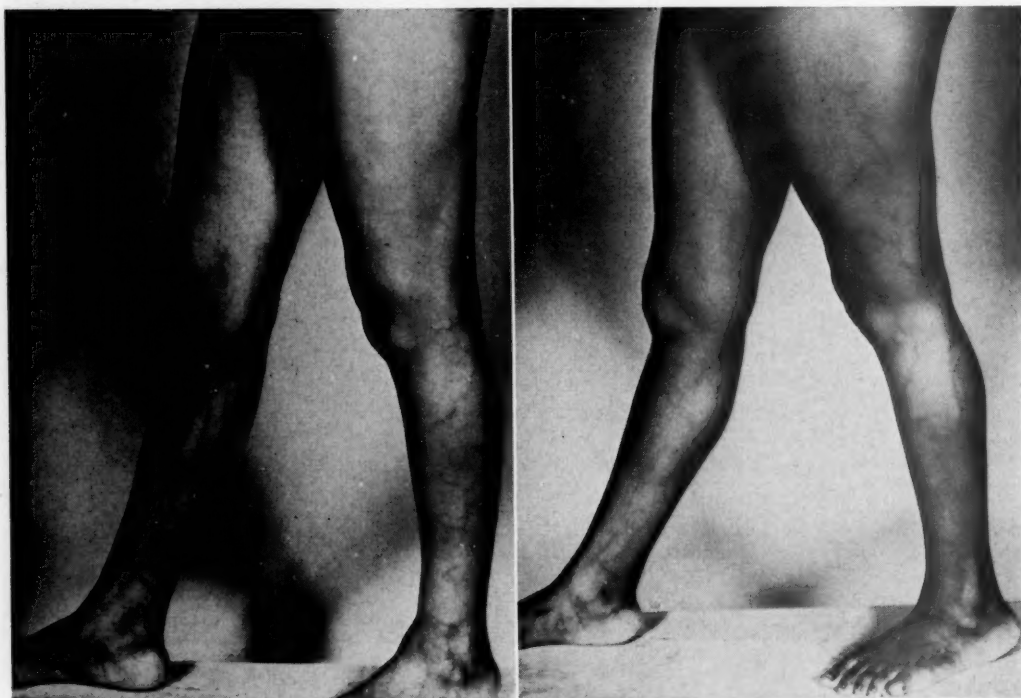
Fig. 7.—A, Infrared photograph of leg veins, anterior view, of patient who had ligation, now 32 weeks pregnant. B, Infrared photograph of leg veins, anterior view, of patient who had not had previous surgery or vascular disease, now 32 weeks pregnant.

### Fetal Mortality

There were 28 single births and one set of twins. Only 2 of the 30 babies did not survive (Table IV). One patient is still pregnant. Twenty-two of the babies were considered to be at term. One of these infants was stillborn. The mother had pre-eclampsia. Eight other infants, including the twins, were premature. One of these premature babies died after an unattended birth in a rural home. We were unable to get details other than that the infant was born alive but died shortly after birth. The heaviest term baby weighed 8 pounds,

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the smallest premature 2 pounds. This infant survived. There was one fetal anomaly, bilateral talipes equinovarus and paraplegia. This child lived to the age of 2 years and died of sepsis and malnutrition. The paraplegia was not considered to be due to birth trauma. Studies at the cerebral palsy center did not disclose the cause and autopsy was not obtained.

TABLE III. TYPE OF DELIVERY

Vaginal	24
Cesarean section (repeat)	4
Cesarean section (primary)	1*
Pregnant at present	1
Total	30

\*Ruptured marginal sinus.

TABLE IV. FETAL MORTALITY

WEEK OF GESTATION	NO. OF INFANTS	DEATHS
<i>Pregnancy Subsequent to Ligation.—</i>		
38-40	22	1 stillbirth (pre-eclampsia)
34-38	7*	1 premature†
28-34	1	0
Total	30	2 (6.67%)
<i>Pregnancy Prior to Ligation.—</i>		
38-40	48	3
28-38	7‡	2
Total	55	5 (9.09%)

\*One set of twins.

†Unattended birth at home.

‡Two sets of twins.

Table IV also reveals the fetal deaths prior to ligation. Only the known preligation neonatal or intrapartal deaths are recorded. A vague history, such as "about 6 months and died," was not used in calculating these mortality rates. We believe there is no statistically significant difference in the results of the number of preligation fetal deaths and the postligation figures (Table IV).

### Abortions

There were 17 abortions in these 47 pregnancies subsequent to ligation of the inferior vena cava and ovarian vessels. One of these was known to have been induced. All these 17 occurred in our 16 Charity Hospital Clinic patients. Thirteen of these occurred in the first pregnancies after ligation and included the aforementioned induced abortion (Fig. 2). All 16 of these women had had severe infection of the uterus and pelvic veins that required the venous ligations. We believe that the effects of the infectious process were more likely the cause of the abortions than the interrupted venous return. Furthermore, when we consider the past obstetrical histories of the 13 patients who had abortions, we find that 9 of these abortions were prior to the ligation, either immediately before or in some previous pregnancies (Table V). We believe that the interrupted venous return was not necessarily the cause of the subsequent unsuccessful pregnancies. An additional support to our belief is the fact that 8 of these women who aborted their first postligation conceptions later had successful pregnancies. We would expect the opposite if pelvic venous hypertension or engorgement were the responsible factor (Fig. 3).

There were no major complications from these 17 abortions. Dilatation and curettage was necessary in 6 instances to complete the abortion. Two

patients required blood transfusions on the basis of their needs as determined by laboratory methods. There was one instance of sepsis. This patient had an induced abortion in the same manner as the one that had led to her vein ligation. No other complications were recorded (Table VI).

TABLE V. NUMBER OF ABORTIONS

STATUS	PRELIGATION		POSTLIGATION	
	NO. OF PREGNANCIES	NO. OF ABORTIONS	NO. OF PREGNANCIES	NO. OF ABORTIONS
Private	8	2*	11	0
Clinic	62	9†	36	17*
Total	70	11	47	17

\*One induced.

†Five induced.

TABLE VI. TREATMENT OF ABORTIONS

Uncomplicated	10
Curettage only	4
Curettage and transfusion	2
Septic	1*
Total	17

\*Induced.

### Summary

Twenty-three women who had ligation of the inferior vena cava and ovarian veins subsequently conceived. There was a total of 47 pregnancies subsequent to ligation. Our observations of these women and a study of their obstetrical records have been reported.

### Conclusions

1. Pregnancy subsequent to ligation of the inferior vena cava and ovarian veins can proceed in a normal fashion. Interruption of the normal venous return from the human female reproductive organs does not influence any subsequent antenatal, intrapartal, or puerperal course.

2. Pregnancy is not contraindicated after ligation of the inferior vena cava and ovarian veins. Special care is not necessary in managing the patients who subsequently conceive.

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### Discussion

DR. JOE V. MEIGS, Boston, Mass.—I had the pleasure some time ago of making rounds at Tulane with Dr. Collins and having some of these patients pointed out to me. I saw some extremely sick patients and some after operation and well on their way to recovery.

Much of the infection must be retroperitoneal alone but there must also be cases of phlebitis in the uterine and tubal walls of a serious type. It seems impossible that there would not be accompanying pelvic peritonitis in many of the cases. The youth of the patients must be the reason for their amazing recovery from the inflammatory process.

Subsequent complications from the vena cava ligation in this group are very few. In our hospital where a good many ligations have been done in an older age group, we have not had the same afterresults. In my own few cases ligation was performed because of phlebitis of the leg in patients in whom an abdominal operation was to be done. The ligation of the vena cava took the place of deep or superficial femoral vein interruption.

I have asked a number of our surgeons interested in circulatory disease their opinion with regard to vena cava ligations. The views were that it should be done in (1) patients with severe pelvic phlebitis who are not properly responding to regular treatment or who are giving off septic emboli, (2) patients with phlegmasia alba dolens who because of pulmonary emboli need a vein ligation and in this condition the usual femoral vein ligation cannot be done, and (3) patients who continue to have pulmonary emboli after an interruption of the femoral veins on both sides. As a matter of fact the number of femoral ligations is but a small percentage of what it was a few years ago.

DR. C. PAUL HODGKINSON, Detroit, Mich.—It is important when appraising the compensating efficiency of the veins of the pelvis and legs, to qualify, in terms of potential impaired vascular function, suppurative thrombophlebitis of the pelvis. Dr. Collins and his associates have repeatedly emphasized that the disease process under question is suppurative pelvic thrombophlebitis and not phlegmasia alba dolens, phlegmasia cerulea dolens, or phlebothrombosis. Ligation of the inferior vena cava and the ovarian vessels was carried out as an adjunctive measure to a therapeutic program of antibiotics, anticoagulants, blood transfusions, etc.; the intent of the procedure was to prevent dissemination of the disease by multiple small septic emboli and not to guard against massive embolism as may occur with phlebothrombosis. Under these conditions Drs. Collins, Bosco, and Cohen's report conclusively shows venous circulation from the legs and pelvis to be unimpeded, in both pregnancy and the nonpregnant state, subsequent to ligation of the vena cava and the ovarian vessels.

Studies previously performed in Henry Ford Hospital on the physiology of the ovarian veins showed that during pregnancy the volume of blood carried by the ovarian veins was increased over 66 times; that phlebectasia was physiologic and was accomplished by the process of hypertrophy of the smooth muscle of the media and not by thinning from passive dilatation; and that venous pressure was unchanged in the ovarian veins during pregnancy, an observation which is in contrast to the threefold increase in venous pressure in the veins of the leg as observed by McLennan. It is possible that the compensating mechanism is not entirely passive, whereby blood is returned to the central circulation during pregnancy after ligation of the ovarian and caval veins.

At Henry Ford Hospital ligation of the inferior vena cava has been practiced three times in relation to pregnancy: one patient with phlegmasia cerulea dolens died; another with phlebothrombosis and pulmonary embolism recovered but has not subsequently become pregnant; the third with phlegmasia alba dolens recovered and experienced a pregnancy 5 years later. In her case, venous compensation was inadequate; her experiences during pregnancy were not so fortunate as those reported by Drs. Collins, Bosco, and Cohen.

M. S., Caucasian, was aged 37, para ii and gravida iii. She was obese and suffered from bilateral varicosities of the saphenous systems. Two weeks after spontaneous delivery she developed bilateral thrombophlebitis. The first pulmonary embolism occurred after 4 days of anticoagulant therapy and paravertebral lumbar sympathetic nerve block. Another pulmonary embolism occurred after 8 days. On the tenth day of therapy a large subcutaneous hemorrhage of the left thigh occurred spontaneously as a complication of anticoagulation therapy; the skin of the thigh sloughed and skin grafting was required. Ligation of the inferior vena cava and the right ovarian vessels was performed after 12 days of treatment. Both internal femoral veins were filled with solid clots which extended into the vena cava to within 1 inch of the right renal vein. No clots were observed in the ovarian vessels. Her convalescence was prolonged, complicated, and incomplete. Edema, brawny induration, and ulceration involved intermittently the skin of both lower legs and of the lower abdomen. After 5 years another pregnancy occurred. During the last 2 months, activities were curtailed greatly because of edema of the legs. The brawny induration of the skin of the lower abdomen was

further complicated by the development of bullous edema. Delivery was spontaneous. Subsequently, her life has been marred severely because of decompensation of the venous circulation of the lower half of her body.

From this experience one wonders if the final result of ligation of the inferior vena cava and the ovarian veins does not depend largely upon the initial condition, rather than upon the procedure alone. Apparently the venous systems of the pelvis and legs can compensate for ligation of the major channels provided the smaller tributaries are not occluded by massive thrombosis. It is important that gynecologists understand the intent of this fine paper by Drs. Collins, Bosco, and Cohen and not transfer promiscuously this experience to pathological conditions of a different category.

DR. FRANK R. SMITH, New York, N. Y.—I would like to mention a patient who had had, 5 years previous to my seeing her, a vena cava ligation for a saddle thrombus. She has had four children but, in spite of failure to use contraceptives, she did not become pregnant. Five years later, when I saw her, she also had diabetes.

Because of hemorrhage from the uterus, a curettage was done, and, this failing to produce a cure, a hysterectomy was carried out. At the time of operation, the uterus looked like a hobnailed liver with small subserosal dilated venous sinuses. The broad ligaments had the appearance of a Medusa's head with varicosities as big as the human fist. At that time the empty bladder appeared normal.

About a year later, however, she began to hemorrhage from the bladder, and cystoscopy showed the same process going on in the bladder. The urologists have treated her conservatively and she seems to go along with occasional bouts of hematuria.

DR. COLLINS (Closing).—We'd like to emphasize that these patients had their original inferior vena cava ligation and ovarian vein ligation for severe suppurative pelvic thrombophlebitis that was not responding to other measures or for pulmonary infarction.

We have had a number of these patients subsequently come to hysterectomy and have in the records our findings including some phlebograms. At cesarean section in these 5 instances the operators noted—these were operators whose names do not appear on this paper—that there was no undue dilation of the vessels of the abdominal wall or of the parametrium.



## THE MEASUREMENT OF BLOOD LOST DURING CESAREAN SECTION\*†

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THIS study constitutes an attempt to quantitate the volume of blood lost by a group of patients undergoing cesarean section. In this study a newer technique for the measurement of blood loss was employed.

During cesarean section the bleeding at times is excessive. Estimation of this loss is more difficult than estimation of comparable vaginal hemorrhage because of the greater dispersion of the lost blood. Dieckmann and Daily<sup>1</sup> found the loss to vary from 170 to 1,410 c.c. in 20 patients, with an average loss of 547 c.c. Fifteen years later Dieckmann, with Stout,<sup>2</sup> repeated this study on six patients undergoing cesarean section and found the average loss to be 618 c.c. In the series of eight patients studied by Tatum<sup>3</sup> in 1953, the average loss was even greater—923 c.c.

Attempts at estimation of loss of blood during operations have been made many times. The reason is not merely academic, for the postoperative progress is often retarded by excessive loss of blood, and replacement of blood can be planned more precisely if the amount of bleeding is known.

Four methods are commonly used to measure loss of blood. First is direct measurement of the blood in basins and the like. This is uniquely suited to vaginal deliveries.

Second is the photometric technique. Gatch and Little,<sup>3</sup> in 1924, converted blood pigment to acid hematin and compared the concentration with the patient's own venous blood. Dieckmann and Daily<sup>1</sup> elaborated the technique and increased its precision. Use of a spectrophotometer and measurement of the blood as oxyhemoglobin were proposed by Pileher and Sheard.<sup>6</sup>

Third is a gravimetric procedure. As introduced by Wangenstein,<sup>10</sup> this technique depends upon the increase in weight of sponges during an operation, the increase being converted to cubic centimeters of blood on a cubic centimeter per gram basis.

\*Abridgment of thesis submitted by Dr. Wilcox to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Obstetrics and Gynecology.

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‡The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Fourth is the volumetric method. The patient's plasma or erythrocytes are labeled with dyes or radioactive substances, and the reduction in the blood volume during the operation is calculated.

The error of these methods, when they are meticulously performed, is generally small. Representative values for error which have been reported are: 5 per cent for the photometric method with acid hematin<sup>3</sup> or oxyhemoglobin,<sup>9</sup> 3 per cent with a cyanmethemoglobin variation,<sup>4</sup> and as low as 2 per cent<sup>5</sup> if the sponges are rinsed twice. These errors refer strictly to the detection of blood in salvaged sponges and toweling, and do not include unrecognized spilling of blood at the time of the operation.

### Method

Quantitation of loss of blood was based on the method of Pilcher and Sheard,<sup>6</sup> adapted from Gores'<sup>4</sup> modification.

A tenth of a cubic centimeter of a specimen of the patient's blood, taken preoperatively and accurately measured, was added to 20 c.c. of an aqueous solution of sodium cyanide (100 mg. per liter) and potassium ferricyanide (300 mg. per liter). The resulting cyanmethemoglobin was measured in a Sheard-Sanford photometer<sup>7</sup> with a standard green filter. The light transmission of any specimen was compared with a standard curve based on the average of several samples of blood of which the oxygen capacity had been determined. The result was recorded in terms of grams of hemoglobin per 100 ml. of blood. Five replicates were averaged to determine the patient's preoperative value for hemoglobin.

In the case of blood lost at operation, all sponges, wound towels, and other stained linen were placed in an electric washing machine and agitated for at least 3 hours with added water. The water was collected directly from the machine, from the cloths, which were put through a wringer, and from the blood collected by aspiration during the operation. At the suggestion of Dr. T. B. Magath, Section of Clinical Pathology of the Mayo Clinic, it was found that the amount of water retained in the wrung sponges was sufficiently constant to permit application of a simple correction factor rather than to weigh these sponges individually and then to subtract the dry weights.

*Use of This Method.*—Because of the extensive dilution of the solution of hemoglobin, the addition of 0.1 c.c. to the 20 c.c. of cyanide reagent gave too weak a concentration of cyanmethemoglobin to be read accurately in the photometer. Accordingly, the dilute hemoglobin solution was clarified by centrifugation and 2 c.c. was added to the 20 c.c. of solution of cyanide. Thus, instead of the usual 1:201 dilution, a 1:11 dilution was obtained. The concentration of hemoglobin obtained, expressed as grams per 100 ml. from the standard curve, was multiplied by 11/201 to correct for this modification of the standard technique. As an example (Case 21):

Patient's value for hemoglobin (average of five determinations): 11.9 Gm. per 100 c.c.

Total volume of blood lost plus added water: 22,574 c.c.

Apparent hemoglobin content of the "lost blood" (average of five determinations): 11.66 Gm. per 100 c.c.

Corrected ( $\times 11/201$ ) hemoglobin in "lost blood": 0.627 Gm. per 100 c.c.

Total hemoglobin in "lost blood" ( $22,574 \times 0.627$ ): 14,154 Gm.

Blood loss (hemoglobin recovered/blood hemoglobin): 1,189 c.c.

TABLE I. LOSS OF BLOOD DURING CESAREAN SECTION: 25 PATIENTS

CASE	GRAVIDITY	PARITY	GESTATION (WEEKS)	LABOR (HOURS)	CESAREAN SECTION, INDICATIONS	SECTION (TYPE)	ANES- THESIA	DURING OPERATION	
								BLOOD PRESSURE (MM. Hg)	BLOOD LOSS (c.c.)
1	iv	ii	33	None	Placenta previa; hemorrhage; prolapsed cord	Classical	Local	120-100/70	274
2	ii	0	42	32	Test of labor; cephalopelvic disproportion; secondary infertility	Low cervical	General	120/70	371
3	i	0	42	10	Trial of labor; elderly primipara; primary infertility	Low cervical	Spinal	160/60	534
4	iii	i	40	None	One previous cesarean section	Low cervical	Local	118/70	577
5	iii	ii	38	None	Two previous cesarean sections	Low cervical	Local	140/70	598
6	viii	iii	37	None	Four previous cesarean sections	Classical	Local	138-120/80	648
7	iii	i	39	None	One previous cesarean section	Low cervical	Local	140/80	694
8	vi	i	38	None	Three previous cesarean sections	Classical	Local	110/70	791
9	i	0	33	None	Progressive toxemia	Low cervical	Local	140/100	802
10	ii	i	37	None	One previous cesarean section	Low cervical	Local	120/70	841
11	iv	iii	39	None	Three previous cesarean sections	Low cervical	Local	130/80	845
12	i	0	34	None	Diabetes 22 years; hydramnios; uncontrolled toxemia	Low cervical	Local	120/70	886
13	i	0	40	19	Test of labor; midplane arrest	Low cervical	General	170/110	940
14	ii	0	39	None	Breech; elderly primipara; secondary infertility	Classical	Local	140/70	1,042
15	ii	i	38	None	One previous cesarean section	Low cervical	Local	110/70	1,050
16	i	0	37	None	Diabetes 14 years; hydramnios, uncontrolled toxemia	Low cervical	Local	130/60	1,052
17	ii	i	38	None	One previous cesarean section	Low cervical	Local	130/80	1,068
18	vi	iv	36	None	Diabetes (gravidia iv); fourth child still-born	Low cervical	Local	120/70	1,074
19	ii	i	38	None	One previous cesarean section	Low cervical	Local	130/70	1,076
20	i	0	38	None	Primary infertility; previous myomectomy	Classical	Local	130/70	1,140
21	iii	ii	36	None	One previous cesarean section	Low cervical	Spinal	120/70	1,189
22	v	iii	34	None	Diabetes; transverse presentation	Classical	Local	160/100	1,545
23	ii	i	40	13	Trial of labor; military attitude; large infant	Low cervical	Local	160-130/85	1,661
24	iv	iii	38	None	Two previous cesarean sections	Low cervical	Local	140/90	1,842
25	v	iii	39	None	Two previous cesarean sections	Low cervical	Local	140-100/70	3,180

To check further the accuracy of the cyanmethemoglobin method, 2 patients, undergoing radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix, were studied with a radioactive chromium technique. Shortly before operation the patients' erythrocytes were labeled with  $\text{Cr}^{51}$  and the washed tagged cells were returned to the patient. Radioactivity of the lost blood was measured and compared with the hemoglobin in the same solution. In one patient the results of the  $\text{Cr}^{51}$  and cyanmethemoglobin methods differed by 1.0 per cent (1,154 c.c. blood loss) and in the other by 4.9 per cent (841 c.c. loss). This degree of accuracy compares favorably with that of other technical procedures in published reports.

An additional test of the method was the determination by one of us (Wilcox) of two specimens of an unknown quantity of blood mixed with known volumes of water and treated in the identical manner with that lost at cesarean section. The results of these determinations revealed an error of less than 1 per cent, being 1,058 c.c. of 1,060 c.c. and 734 c.c. of 740 c.c., respectively.

### Procedure

Twenty-five cases of cesarean section were evaluated in this study. Twenty-one sections were performed by seven members of the obstetric staff and four by graduate fellows in training. Twelve of the patients underwent primary section and 13 underwent repeat section. Four of the 12 patients who had undergone primary section had experienced a trial or test of labor ranging from 10 to 32 hours. None of the patients for whom repeat section was done had been in labor. In six of the cesarean sections a classic incision was employed; in the remaining 19 the section was classified as low cervical.

Fourteen of the patients had reached a gestation time of 38 to 42 weeks; in 7 the gestation was from 36 to 38 weeks, and in 4 it was from 32 to 36 weeks.

Twenty-one of the operations were performed with the aid of local anesthesia supplemented by thiopental sodium, nitrous oxide with ethylene, or simply ethylene. For 2 patients spinal anesthesia was used and for 2 others general anesthesia was employed (for one, ether anesthesia; for the other, anesthesia with nitrous oxide and ethylene).

The technique employed in low cervical cesarean section included vertical incision of the lower uterine segment and a portion of the upper uterine segment in several instances in which the patient had not been in labor. The oxytocic agent employed was ergonovine or methylergonovine tartrate (Methergine tartrate), 0.2 mg. administered intravenously. Oxytocin (pitocin) usually was administered intramuscularly but seldom into the uterus. A uterine pack was utilized in 5 cases. Both low cervical and classic incisions were closed with interrupted mattress sutures followed by a Lembert approximation of the surface edges.

### Results

The results of this study are summarized in Table I.

The minimal loss of measured blood in this series was 274 c.c. (Case 1). The patient was a 25-year-old gravida iv, para ii, who entered the hospital at 33 weeks' gestation with ruptured membranes; she had lost an estimated 1,200 c.c. of blood as a result of partial placenta previa. Sterile vaginal examination revealed a prolapsed cord in addition to the palpable placenta, and a classic cesarean section was performed immediately. A viable male infant weighing 1,820 Gm. (4 pounds) was obtained and he survived. The uterus at the time it was incised appeared to be ischemic, and so little blood was lost that none was collected in the aspirator bottle.



The maximal loss of blood was 3,180 c.c. (Case 25). This occurred in a 25-year-old gravida v, para iii, who previously had undergone two low cervical cesarean sections. The initial section was performed after a failed test of labor in her third pregnancy. The first delivery (elsewhere) was operative and the infant died after a difficult birth. The second pregnancy ended in abortion at 2 months. The patient was admitted to the hospital at 39 weeks' gestation for elective low cervical cesarean section which was performed by one of the obstetric fellows under the supervision of a staff obstetrician. Excessive bleeding from the upper end of the uterine incision at the site of placental implantation was encountered. The uterus was packed and kept under observation, rather than being immediately closed, because the exact origin of the bleeding at first was not apparent. The bleeding was controlled with closure of the wound. Whole blood to the amount of 1,000 c.c. was administered during operation, and an additional 1,000 c.c. was given postoperatively. During the operation the systolic blood pressure decreased from 140 to 100 mm. Hg; the average diastolic pressure was 70 mm. Hg. The postoperative course was uneventful. It is interesting to note that although this operation was the twenty-fourth of the 25 cesarean sections in this series and that we were cognizant of excessive loss of blood, the clinical estimations nonetheless varied from 1,200 to 1,800 c.c. less than the actual measurement.

The average loss of blood for the entire series was 1,028 c.c.; the midvalue (or median) was 940 c.c., suggesting that the average value was not seriously weighted by the loss of blood on the part of the only patient who lost more than 2 liters of blood. Actually, when the patients are classified according to losses of blood at 100 c.c. intervals, the largest group (the mode) is constituted by those who lost 1,000 to 1,100 c.c. Fifty-two per cent of the 25 patients lost less than 1 L. of blood; 48 per cent lost more than 1 L.

The average loss of blood sustained during the 12 primary cesarean sections was 943 c.c. Four of these patients had been in labor, and the average loss of blood among this group was 877 c.c. as compared to 978 c.c. for the 8 patients not in labor.

The average loss of blood during the 13 repeat cesarean sections was 1,108 c.c. Six of the patients concerned had undergone two or more previous cesarean sections and a sharp increase was noted in the loss of blood (1,317 c.c.) in this group, compared to the loss of blood (928 c.c.) in the 7 cases in which only one previous cesarean section had been performed.

The average loss of blood in the 6 classic sections was 906 c.c. In the 19 low cervical sections the loss of blood averaged 1,067 c.c.

Three patients in the entire group of 25 experienced postoperative morbidity, but in none of these was the temperature elevated above 100.4° F. beyond the third postoperative day. There was no apparent relationship between the loss of blood and the morbidity. Two of the patients had been in labor, with ruptured membranes. In no case was the hospital stay prolonged.

Thirteen of the 25 patients received blood during operation.

The average clinical estimate of loss of blood was 325 c.c. less than the actual amount measured. In only 3 cases was the estimate greater than the measured loss.

### Comment

As many investigators have shown previously, this study confirms the pronounced tendency on the part of the surgeon and his associates to underestimate the amount of blood lost at operation. It is difficult to determine accurately by visual methods blood lost in this manner, and the greater the loss the greater is this margin of error. We agree with Dieckmann and Daily<sup>1</sup> that "The

amount of blood which may be lost in a cesarean section performed by an experienced surgeon is astounding. None of the staff realized that the blood loss was more than 700 c.c. in seven out of twenty operations."

One of the reasons for this tendency toward underestimation is the fact that frequently the aspirator bottle is not watched closely. That is, it is not uncommon to observe clean drapes surrounding a freshly closed abdominal incision and then discover 800 to 1,000 c.c. of blood in the aspirator bottle. The old saying, "out of sight, out of mind," undoubtedly is applicable in this instance.

Experience repeatedly has exposed our natural desire to minimize loss of blood. Unconsciously we do not want it to occur, and our estimations appear to reflect this understandable but illogical attitude.

It is surprising, again, to discover how much blood can be absorbed into the linens. For example, the eight-ply Ray-tec gauze sponge 4 by 4 inches when soaked and put through a wringer contains only 3 c.c. of fluid, but a wound towel  $16\frac{3}{4}$  by  $16\frac{3}{4}$  by  $\frac{1}{16}$  inches contains 43 c.c. of fluid, a 12 by 13 by  $\frac{1}{8}$  inches laparotomy sponge absorbs 56 c.c. of fluid, and an ordinary operative towel 18 by 30 by  $\frac{1}{32}$  inches retains 116 c.c. of fluid.

It is important to recall that almost half of the 25 patients who underwent cesarean section in this series lost more than 1,000 c.c. of blood. Fifty-two per cent of these patients received blood during or after the operation. In a similar group of cesarean sections performed prior to this study the incidence of occasions on which blood was required was only 31 per cent.

Although the series is small, it shows that apparently there is a significant increase in loss of blood as repeated sections are performed. This increase is most marked in those patients who have undergone two previous cesarean sections. Some speculative reasons for this may be given. Adhesions certainly are a factor, since they require more time for anatomic dissection.

The experience of the surgeon is one of the most important factors in loss of blood, as this study clearly indicates. The average loss of blood during the cesarean sections performed by the obstetric staff was significantly less than it was when section was performed by resident physicians in training.

Although Dieckmann and Daily felt that their figures were at least 10 per cent too low (546.7 c.c. average), the results of this study (1,028 c.c.) are still significantly higher. This figure is somewhat closer to that reported by Tatum (923 c.c.).

The modification of technique employed in this study is of value in accurate determination of blood lost in extensive procedures. The counting of a large number of sponges, the average retention capacities of which are known, permits accurate determination of the fluid which cannot be measured directly. The large dilution factor, as high as 1 in 30, permits the loss or error of as much as 30 c.c. of fluid for 1 c.c. of blood. It also was found that there is less tendency for discrepancies in determination of hemoglobin when this dilute solution is employed. The method is not suitable for the everyday estimation of blood lost in the operating room, because it is a time-consuming, exacting procedure. The value of the method for research purposes has been demonstrated.

It should be emphasized that in all cases determinations of the quantity of blood lost are less than the actual amount lost, for despite careful efforts it is mechanically impossible to collect all the blood lost at the time of cesarean section.

### Summary

1. A modification of the cyanmethemoglobin photometric method of determining loss of blood has been introduced. It is hoped that this method will

be of value in increasing the accuracy of future investigation and at the same time save many hours of tedious work.

2. The operative bleeding of 25 patients who underwent cesarean section was studied; the average loss of blood was 1,028 c.c. The minimal loss of blood was 274 c.c. and the maximal loss was 3,180 c.c. The median was 940 c.c. Forty-eight per cent of patients lost more than 1,000 c.c. of blood.

3. The experience of the surgeon is believed to be one of the significant factors in maintaining a minimal loss of blood.

4. It is impossible to guess with accuracy the quantity of blood lost at operation. Some of the factors responsible for this discrepancy have been elaborated.

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#### Discussion

DR. ABRAHAM F. LASH, Chicago, Ill.—The essayists have presented a research method for the determination of blood loss during cesarean section. This modification of the technique of Pilcher and Sheard (spectrophotometer) is superior to the other methods because it yields an error of less than 1.0 per cent as compared to the 3.0 to 5.0 per cent of the other methods. The importance of this carefully executed and time-consuming study is that it again directs attention to the disparity between estimated and properly measured loss of blood.

Therefore, the lesson to be derived from this study is the need to anticipate the blood loss in cesarean section. The practical suggestion to watch the collecting bottle from the aspirator (by operator, assistants, anesthetist, and nurses) and observe the linen and sponges may be based on this scientific study. Thus the anesthetist or a nurse may well tabulate roughly total blood loss. It is important to have some estimate of blood loss, not only to allow for replacement but to avoid overloading the circulation by too rapid infusion.

Repeat cesarean sections have apparently a higher blood loss than primary sections. This finding, as well as other drawbacks, gives further reason for more thoughtful consideration of the so-called simple and safe cesarean section.

At Michael Reese and Cook County Hospitals we not only underestimate blood loss but also overestimate weights and sizes of babies. There seems to be a trend toward allowing previous cesarean section patients to go into labor in order to get full-term babies, to determine whether repeat section is necessary and to prevent blood loss. With two or more previous cesarean sections, however, no one would risk a vaginal delivery, and everyone should be alert to replace blood loss.

DR. JOSEPH A. HARDY, St. Louis, Mo.—Even in this enlightened age, there is a tendency to accept blood loss as a usual accompaniment of cesarean section. We are likely to underestimate, sometimes seriously, the amount of such blood loss.

\*Complete references for the longer version of this work, which was a master's thesis, can be had by consulting the original thesis on file in both the University of Minnesota Library and the Armed Forces Medical Library in Washington, D. C.



The various methods of measuring, more or less accurately, the amount of blood loss have been reviewed. It appears that the photometric technique used by the authors provides a reliable, if cumbersome, means of determining the degree to which the patient who has had a cesarean section has suffered in this regard. The method is admittedly not adapted to use in the average general or private maternity hospital. This, however, does not in any way detract from its significance. If, as a result of Dr. Hunt's admonitions, we are made more aware of the importance of conserving blood during abdominal delivery, an excellent purpose has been served.

I have reviewed the 89 cesarean sections done during the year 1957 at St. Mary's Hospital, St. Louis. St. Mary's is the private patient department of the St. Louis University Hospitals and these 89 caesarean sections (done in the course of 4,124 deliveries—an incidence of 2.1 per cent) were performed by 14 obstetricians, all members of the faculty of St. Louis University School of Medicine.

Since no actual measurement of blood loss had been made, I attempted to relate antepartum blood levels, as reflected in hemoglobin and hematocrit determinations, with similar determinations made preoperatively and on the third day postpartum. I attempted to correlate the obstetricians' estimate of blood loss during section with the observable drop in hemoglobin and hematocrit levels postoperatively. I also noted the frequency with which patients were transfused. My analysis was certainly crude—but it was remarkably informative.

In 6 cases in which the obstetrician's estimate of blood loss was "moderate" or "slight," the postpartum hemoglobin levels had dropped to 10.6, 10.2, 10.4, 10.4, and 9.8 Gm., respectively. In none of these instances had the preoperative hemoglobin determination been less than 11.7 Gm. Obviously, even the experienced obstetrician may at times grossly underestimate the amount of blood spilled during his operative procedure.

Thirty-eight of these 89 patients undergoing cesarean section received one or more transfusions (the maximum was 4 transfusions). But here again a disturbing fact comes to light. There were 23 patients who exhibited a drop in hemoglobin below 11 Gm. on the third day after operation. But only 13 of these acutely anemic patients received a transfusion during their stay in the hospital.

DR. HUNT (Closing).—Perhaps some of you think that we do rather clumsy cesarean sections on our service because of the blood loss. We are occasional operators, our service is small, and there are residents to train. Several of us do the cesarean sections, and our section rate is not high. On the other hand, except for one section done post mortem and one on a patient who died 5 weeks postpartum from a bizarre type of purpura from hypersplenism, our last cesarean section death was in 1933.

None of the babies was lost. We try to bring the patients to term, in so far as possible, without their going into labor. This subject was discussed in relation to Dr. Diddle's paper, and he and his discussants were properly concerned about the deaths from prematurity of repeat section. Some of our patients were operated on prematurely but only for such obstetric reasons as severe diabetes and placenta previa.

Dr. Hardy observed that his third-day hemoglobin determinations were a rough measurement of blood loss, and in this I concur. If we take the old rough rule of a decrease of 1 Gm. as representing a blood loss of  $\frac{1}{2}$  L., his average blood loss was about 1 L. One of his patients showed a drop from 14.2 to 9.0, which would represent about  $2\frac{1}{2}$  L. blood loss. In another way he has shown that these patients lose a lot of blood. The non-contracting uterus at term is a very vascular organ.



## EVALUATION OF CHEMOTHERAPY IN OVARIAN AND CERVICAL CANCER BY TISSUE CULTURE METHODS\*†

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PROBABLY no aspect of biologic research is being carried on with more vigor at the moment than that involving the evaluation of carcinolytic compounds. With the use of antibiotics in the past decade, it has been possible to extend the methods of long-term tissue culture to a wide variety of human and experimental neoplasms. Also, the use of cortisone has facilitated the successful transfer of human cancers to experimental animals. As a result, the literature is filled with reports concerning the effect of chemotherapeutic compounds on malignant neoplasms growing in tissue culture, in experimental animals, and in human patients.

A great many compounds, including nitrogen mustard derivatives, folic acid analogues, and the purine derivatives, have been used clinically with varying but minor degrees of success. The concept of prophylactic chemotherapy at the time of cancer surgery has been seriously considered by those noting the high incidence of malignant cells in the peripheral blood sampled at operation.<sup>1, 2</sup> A unique though notable success has been reported with the use of Methotrexate in choriocarcinoma.<sup>3</sup> Such innovations stimulated by basic in vitro and in vivo investigation are extending our clinical experience with greater frequency. Thus, it seems increasingly essential that gynecologists keep pace with the methods which lead to such clinical application.

The experience of the various groups utilizing cancer chemotherapy on a clinical basis has generally not led to enthusiastic acceptance. We have had some experience in the use of thioTEPA, dimethyl Myleran, and chlorambucil in the treatment of uterine and ovarian carcinoma. In each case the drug was used in association with other methods of treatment or as a last resort. In isolated instances, substantial palliative success has resulted. Undoubtedly, a large number of patients treated with these drugs will be required to establish the significance of the results. The Cancer Chemotherapy National Service Center has recently endeavored to standardize the use of these compounds by recognized clinics throughout the nation and to evaluate the experience on a wider scale.

\*This investigation was supported by research grant No. C-2413 (C<sub>2</sub>) from the National Institutes of Health, United States Public Health Service.

†Presented at the Sixty-ninth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 4-6, 1958.

\*\*Medical Student Research Fellow, American Cancer Society.

In an effort to gain additional knowledge concerning the effect of these carcinolytic compounds, we have turned to human strains of uterine and ovarian carcinoma growing in tissue culture. We have endeavored to evaluate the effect of the three drugs (Fig. 1) with which we have had some clinical experience, on cervical and ovarian cancer cells growing in culture at constant and predictable rates.

### Methods and Materials

**Maintenance of Stock Cultures.**—Cells were grown in vitro directly upon the glass substrate of square screw-cap 200 ml. bottles. The growth medium employed consisted of a mixture of adult human serum 28 per cent, tryptose phosphate broth 23 per cent, yeast extract 6.9 per cent, glucose 2 per cent, bicarbonate 0.1 per cent, and physiologic salt solution (Hanks's) 40 per cent.\* The culture bottles were placed in stationary, horizontal positions permitting 10 ml. of feeding solution to cover fully the cellular layer and were incubated at 36.5° C. The cultures were refed on the third day following initial cultivation, and when confluent growth was present, usually by the twelfth day, they were considered ready for subculturing.

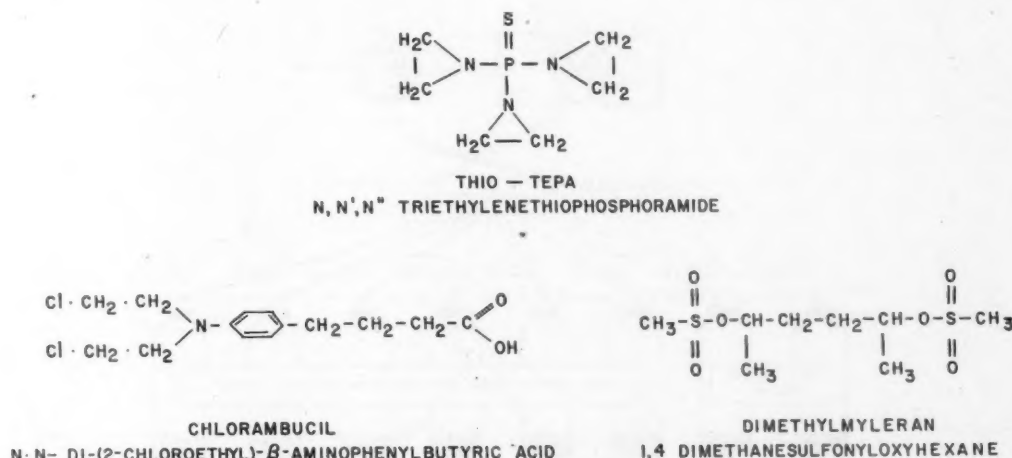


Fig. 1.—Formulas of thioTEPA, chlorambucil, and dimethyl Myleran.

**Preparation of Replicate Cultures.**—A stock bottle was selected which microscopically appeared to be confluent with healthy-appearing cells (Fig. 2). After the growth medium was drawn off, the cell layer was washed with two 5 ml. changes of Saline A† followed by the addition of 5 ml. of 0.25 per cent trypsin (1:300) in Saline A. With a bent-tip pipette fitted with a bulb, the trypsin solution was repeatedly drawn up and directed against the cell layer until all of the cells had been dislodged from the glass. By continued agitation with the bulb pipette, all cell clumps were divided until a uniform suspension of single cells was effected. The suspension was then transferred to a 15 ml. centrifuge tube and centrifuged for 1 minute at 1,000 r.p.m. The supernatant trypsin solution was discarded, and 1 ml. of Saline A added to the packed cells. Again, by agitation with a bulb pipette, the cells were resuspended in the saline

\*Formula of Dr. Pamela Byatt modified after that of Ginsberg.<sup>4</sup>

†This solution is physiologic saline without calcium, magnesium, and phosphate buffers as described by Puck.<sup>5</sup>

solution until a uniform "cloud" of cells was raised. A drop of the cell suspension was transferred to a hemocytometer and the total number of cells per cubic centimeter calculated. The cells in the centrifuge tube were then diluted with Saline A to provide an inoculum of suitable cell density (usually 1 million cells per 0.5 ml.).

*Preparation of Experiment.*—Following enumeration of cells, culture bottles were inoculated with about 1 million cells (0.5 ml. of the adjusted cell suspension). Ten milliliters of growth medium containing sufficient chemotherapeutic

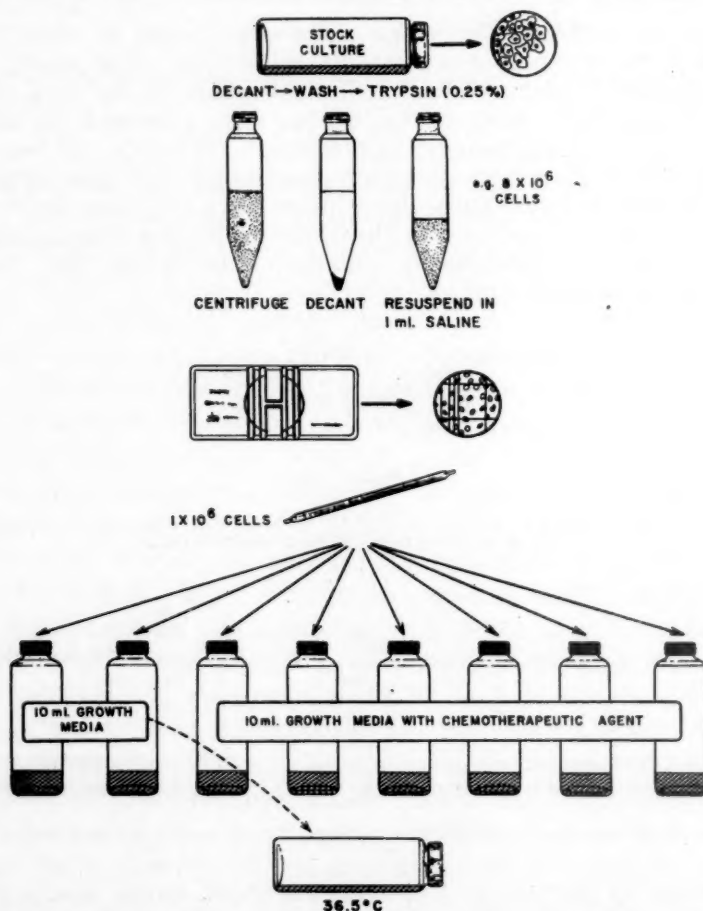


Fig. 2.—Preparation of cultures for cell enumeration experiments.

agent to give the desired concentration was then added to each culture bottle. Concurrently, control cultures were prepared with the same cell population and growth medium, without the aliquot of experimental drug. Following the prescribed period of growth, the experimental and control cultures were again washed with two changes of Saline A, trypsinized, centrifuged, and the packed cells were resuspended in 1 ml. of Saline A and counted in a hemocytometer. Evaluation of the effect of the chemotherapeutic drug was made directly from the enumeration of cells following exposure to the carcinolytic compound. In some instances, wherein the drug under study required a toxic substance to facilitate placing the agent into solution (e.g., methanol to dissolve dimethyl Myleran), an identical volume of solvent was added to the control in the same concentration as used in the experimental cultures. For qualitative evaluation of the expected cytotoxic effect, parallel cultures were made in 60 by 15 mm.

Petri dishes in which one or more coverslips were placed (Fig. 3). The coverslips with the attached growing cells were removed following the prescribed period of growth, and were fixed and stained or studied under phase-contrast microscopy.

Concentrations of chemotherapeutic agent in the growth medium were such that on the basis of knowledge gained from pilot experiments, minimal to devastating effects on the cell cultures could be expected. The carcinolytic compounds were added to the growth media to provide the concentrations indicated in Table I.

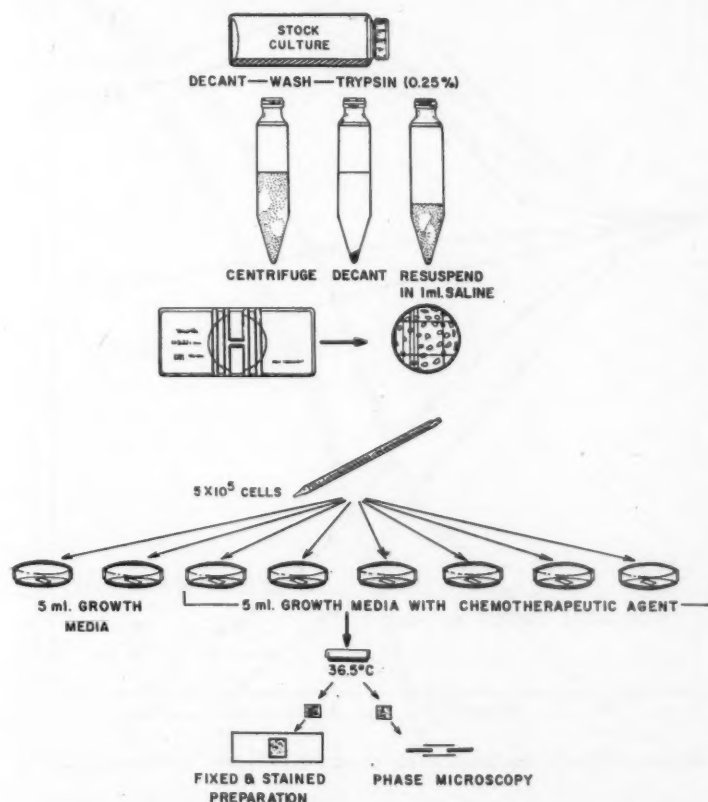


Fig. 3.—Preparation of cultures for cell observation.

TABLE I. CONCENTRATIONS OF CHEMOTHERAPEUTIC AGENTS IN CULTURE MEDIA

thiOTEPA*		DIMETHYL MYLERAN†		CHLORAMBUCIL‡	
MG. PER ML.	MILLIMOLS	MG. PER ML.	MILLIMOLS	MG. PER ML.	MILLIMOLS
0.00125	0.008	0.006	0.02	0.0003	0.001
0.0025	0.015	0.012	0.04	0.0006	0.002
0.005	0.031	0.024	0.09	0.0012	0.004
0.01	0.062	0.048	0.18	0.0024	0.008
0.02	0.123	0.096	0.35	0.0048	0.016

\*Provided through the courtesy of Dr. Carl Ruggsger, Medical Director, Lederle Laboratories, Pearl River, New York.

†Provided through the courtesy of Dr. Geoffrey Timmis and Dr. Alexander Haddow of the Chester Beatty Institute, London, England.

‡Provided through the courtesy of Dr. Donald S. Searle, Medical Director, Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.

Three well-established cell cultures were utilized to test the cytotoxic activity of these compounds in vitro. One was a strain of human amnion cells (Amnion



F.L.) established by the Virus Laboratory at the University of California. The second was the S3 modification of the cervical cancer cell strain (HeLa) established by Dr. George Gey at Johns Hopkins University. The third was an ovarian cancer cell strain (4-58) established in our laboratory. Stock cultures selected for the experiments were healthy in appearance and all populations were growing at predictable and reproducible rates.

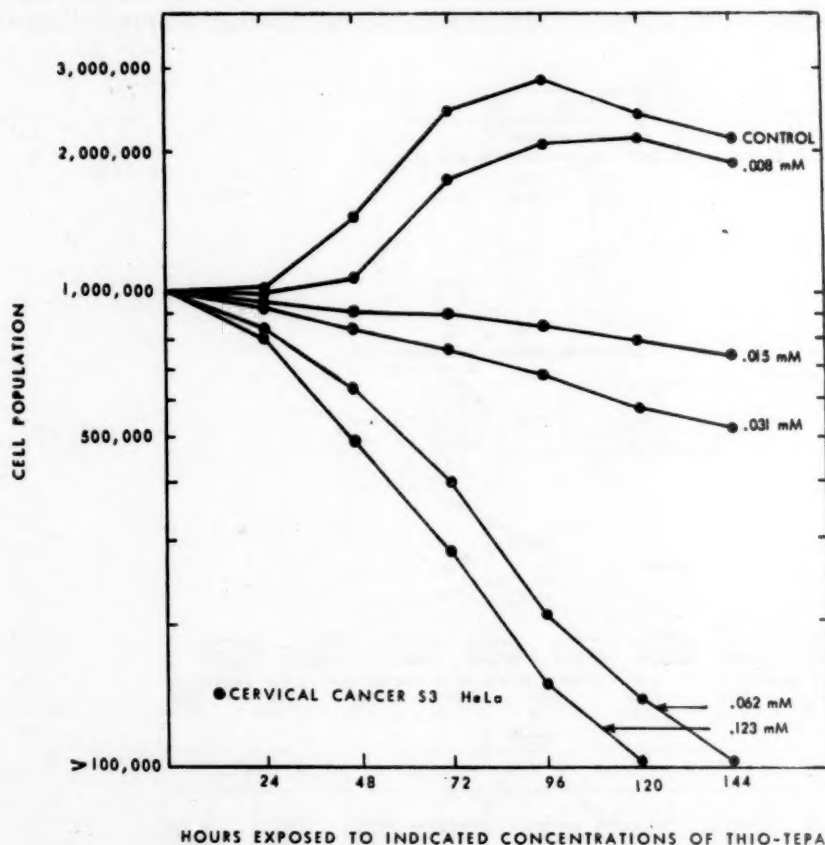


Fig. 4.—The cytotoxic effect at 24 hour intervals of varying concentrations of thioTEPA on S3 HeLa cells in vitro.

### Results

When cervical carcinoma cells (S3 HeLa) were grown in media treated with concentrations of thioTEPA varying from 0.008 mM to 0.12 mM, a wide range of proliferative response was noted (Fig. 4). As might be expected with the lowest concentration, the cell population during each day of culture varied little from that of the untreated control. As the cells were exposed to high concentrations of thioTEPA, the depressant effect on cell reproduction and survival was progressively increased. The maximum variation of cell population was noted on the fifth and sixth days. By the sixth day, cell cultures exposed to the two highest concentrations of thioTEPA were virtually destroyed. In comparing these values, it should be emphasized that each value plotted represents the geometric mean cell population of three cultures for each concentration of drug. Fig. 5 shows the grouping of these values on a larger scale graph and indicates the significant reproducibility of results beyond the first 24 hours of culture.

Fig. 6 shows the effect of thioTEPA in the same concentrations on a strain of cells (Amnion F.L.) derived from nonmalignant tissue. When compared with the cytotoxic effect of thioTEPA on cervical carcinoma cells, the similarity of cell counts is impressive. From these two experiments, it appears that the depressant effect of this compound on the HeLa strain of cells derived from cervical cancer and on cells derived from a normal amnion is of essentially the same magnitude.

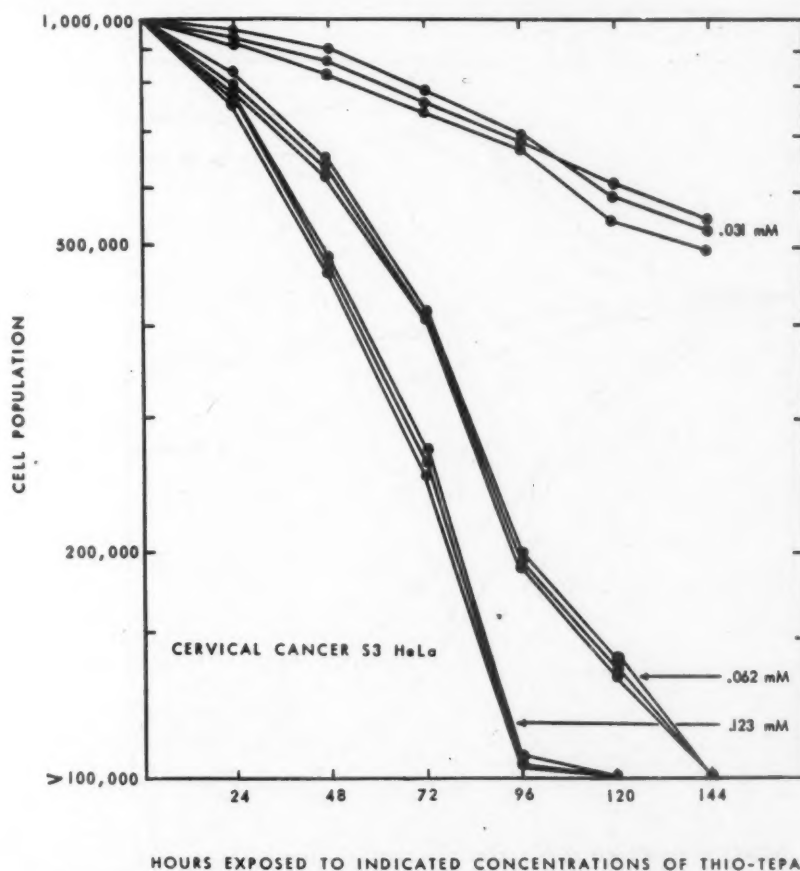


Fig. 5.—Replicate cultures showing the reproducibility of cytotoxic effect as reflected by cell counts.

To assess the effect of thioTEPA on ovarian cancer in vitro, cultures were grown in the presence of the indicated concentrations for 6 days (period of maximum variation). With exposure to increasing concentrations of thioTEPA, the progressive decrease in cell population, expressed in per cent of the number of cells counted in the control cultures, is shown in Fig. 7.

The microscopic appearance of fixed and stained ovarian cancer cell (4-58) cultures exposed to increasing concentrations of thioTEPA is shown in Fig. 8. The decrease in cell population as the concentration of the cytotoxic drug increases is obvious at a casual glance. Closer inspection shows that, as the cells are exposed to higher concentrations of the compound, the nuclei swell, the cytoplasm shrinks with the formation of thin spinous connections between cells, and the medium becomes filled with particulate debris. Under phase-contrast microscopy (Fig. 9) the same changes are seen. In addition, the mitochondria lack proper orientation around the nuclei, cytoplasmic inclusions appear, and increased cellular opacity is noted as the thioTEPA takes effect.

Plotting cell populations of three different human cell strains exposed to increasing concentrations of thioTEPA in culture indicates that the effect is characteristic of the drug and not necessarily of the strain of cells. Thus, Fig. 10 shows that the effects of specific concentrations of thioTEPA on cell reproduction and survival of strains derived from cervical carcinoma, ovarian carcinoma, and normal amnion are practically identical. The  $ID_{50}^*$  value for

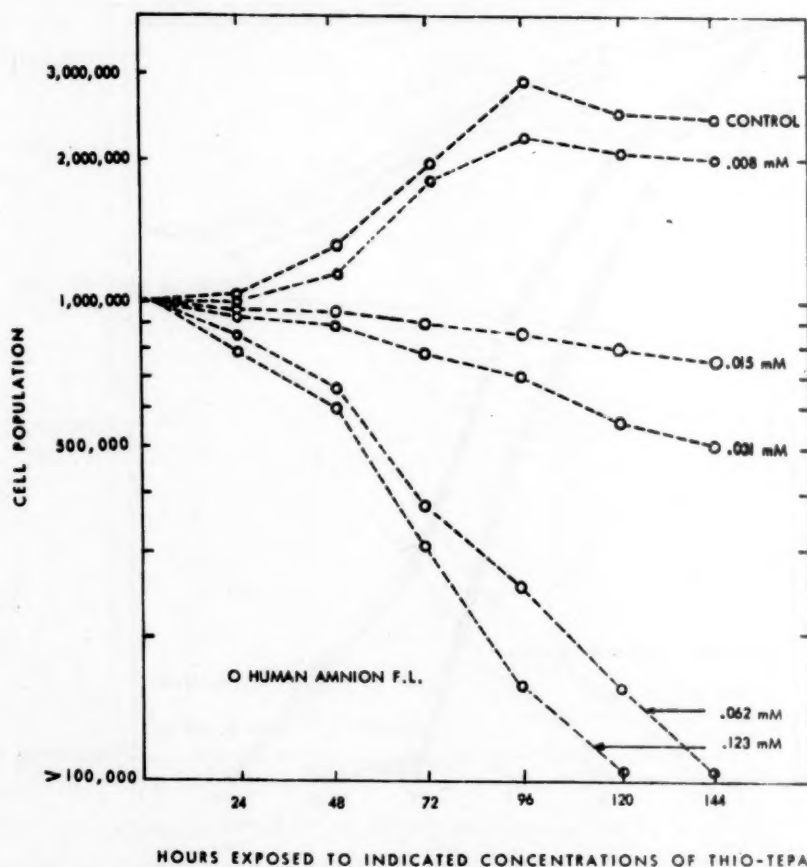


Fig. 6.—The cytotoxic effect at 24 hour intervals of varying concentrations of thioTEPA on Amnion F. L. cells in vitro.

thioTEPA against these strains as interpolated from this graph (Fig. 10) and confirmed by additional culture experiments is 0.012 mM. It seems significant that Eagle and Foley<sup>6</sup> reported the same figure for this value.

Fig. 11 also shows that the three cell strains react similarly to specific concentrations of dimethyl Myleran. Higher millimolar concentrations of this compound were necessary to produce a comparable range of cytotoxic activity than with thioTEPA. Also, the  $ID_{50}$  value for this agent against the three cell strains is 0.03 mM, a higher concentration than was necessary to produce an  $ID_{50}$  effect with thioTEPA. The cell population counts for the three strains exposed to 0.09 mM. of dimethyl Myleran vary sufficiently to lose their statistical significance. The variation in this instance is probably related to difficulty in effecting complete dissolution of the sparingly soluble compound.

\*Concentration of compound which produces a 50 per cent inhibition of growth.

Of the three compounds studied, chlorambucil proved to require the lowest concentration in order to effect a significant cytotoxic effect *in vitro*. This compound, recently recommended for study against ovarian carcinoma by a committee of the Cancer Chemotherapy National Service Center, was added to culture media in which cell strains of ovarian carcinoma (4-58) and normal amnion were grown. Fig. 12 shows the cytotoxic activity of the compound. Note that the  $ID_{50}$  value is .004 mM., a significantly lower concentration than is required by either thioTEPA or dimethyl Myleran.

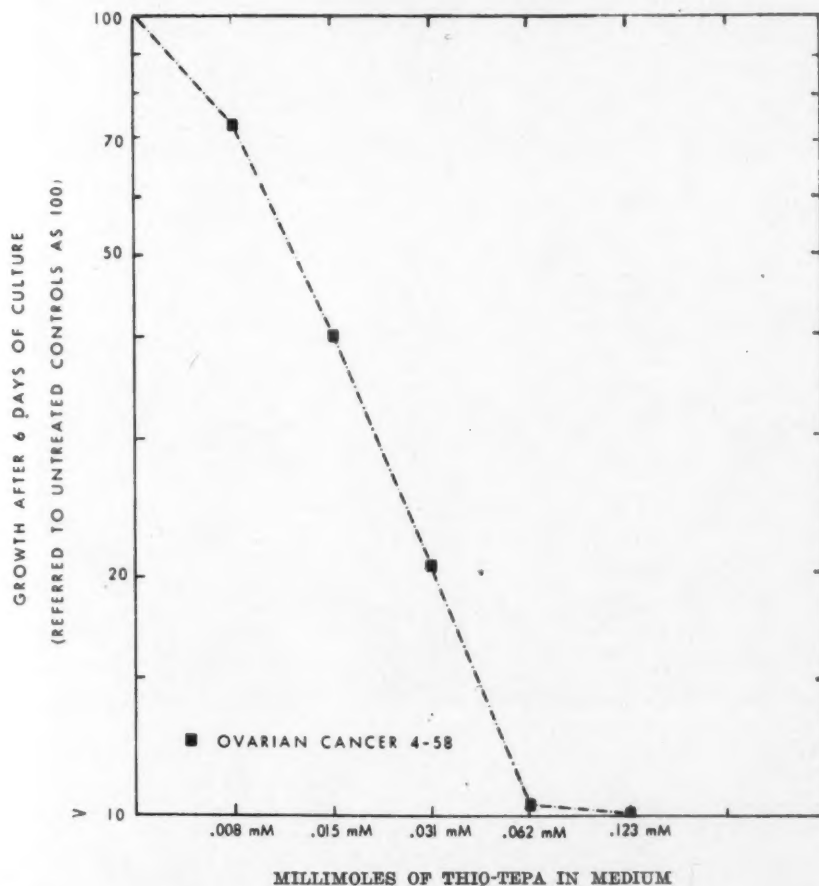


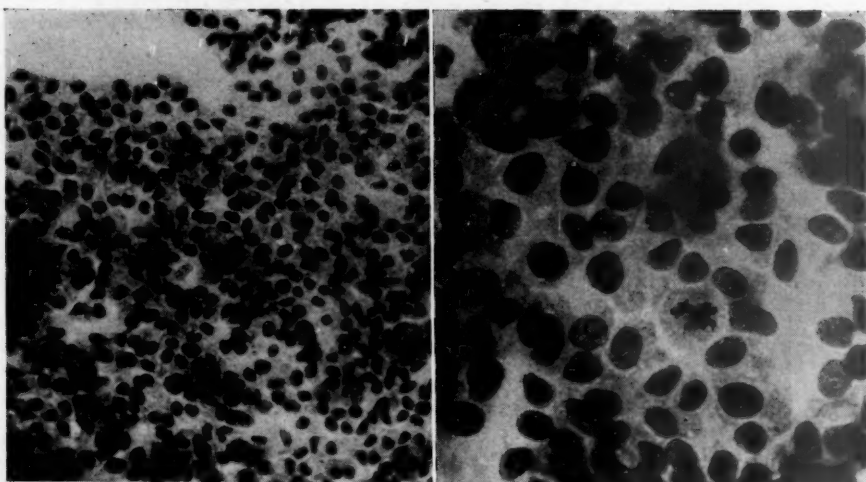
Fig. 7.—The cytotoxic effect after 6 days of thioTEPA on ovarian cancer cell strain 4-58 in *vitro*.

### Comment

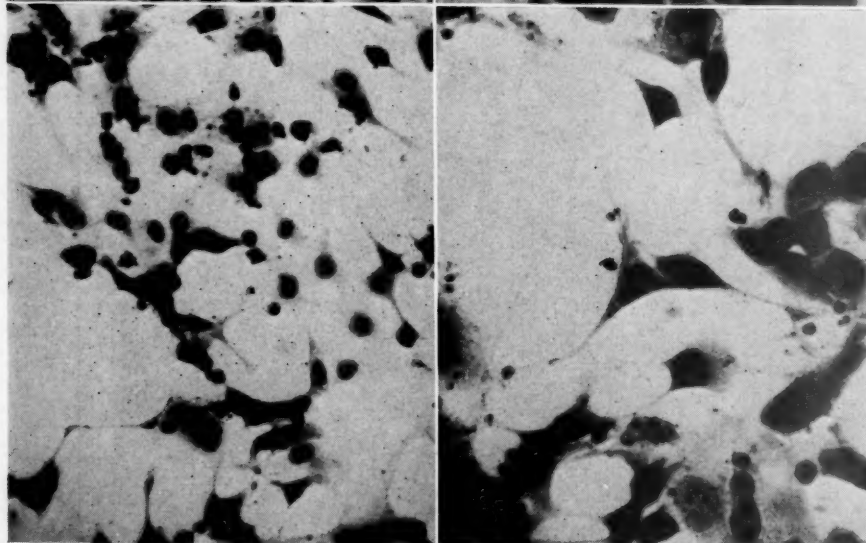
As the investigator surveys the methods of tissue culture as a tool in evaluating cancerolytic compounds he is struck by a number of considerations. First, tissue culture is less expensive and far less time consuming than *in vivo* assays utilizing experimental animals. Human neoplasms growing vigorously in tissue culture are readily available, whereas it is often difficult to effect vigorous transplants in animal hosts. Also, with well-established cell strains, the neoplastic cells can be exposed to exact concentrations of chemotherapeutic agents and mathematically precise results can be observed.



A.



B.



C.

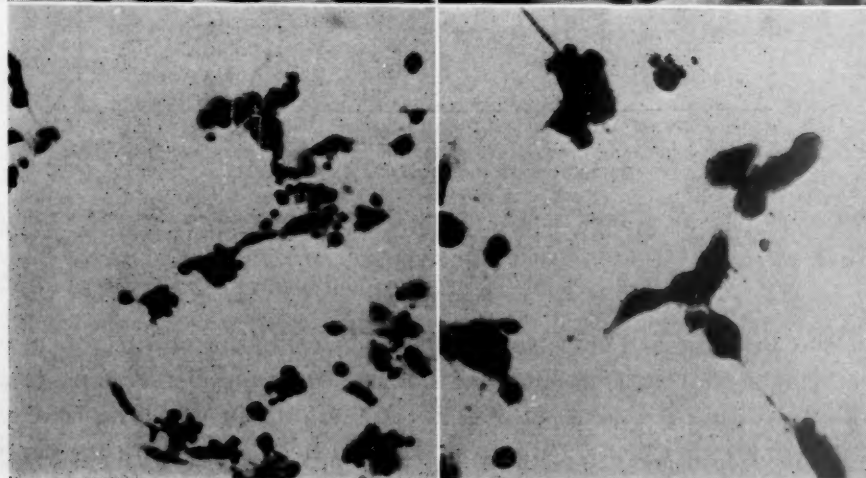


Fig. 8.—Ovarian cancer cells (4-58) after 6 days' exposure in culture to thioTEPA. (Fixed and stained. Left,  $\times 125$ ; right  $\times 312$ ; reduced  $\frac{1}{3}$ .)

A, Control culture.

B, 0.031 mM thioTEPA.

C, 0.062 mM thioTEPA.

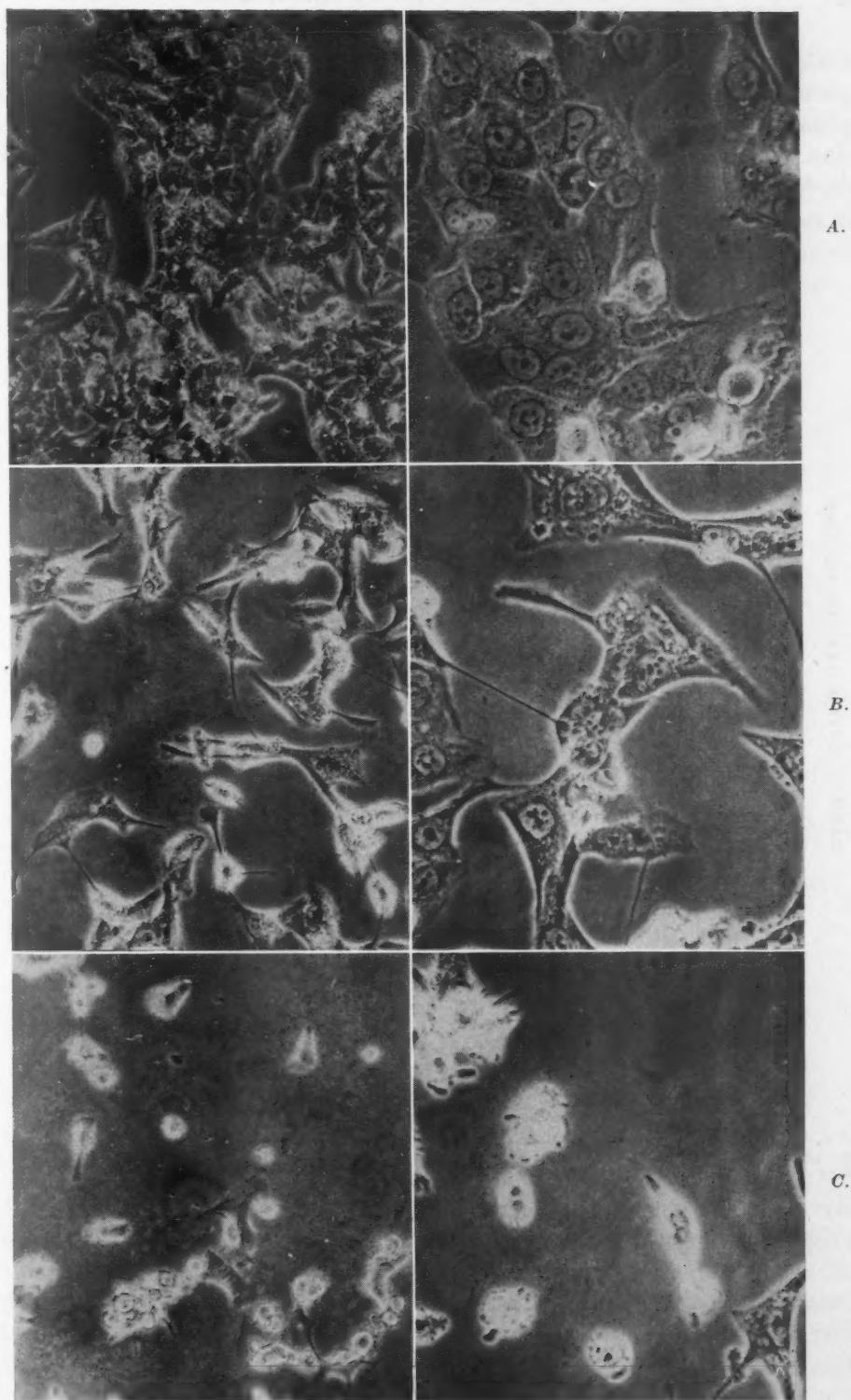


Fig. 9.—Ovarian cancer cells (4-58) after 6 days' exposure to thioTEPA. (Phase contrast. Left,  $\times 125$ ; right,  $\times 312$ ; reduced  $\frac{1}{6}$ .)

A, Control culture.

B, 0.031 mM thioTEPA.

C, 0.062 mM thioTEPA.

Conversely, glaring inadequacies in tissue culture evaluations soon become apparent. In our experience with short-term tissue culture where biopsies are explanted from the host to the test tube, we have found the precarious nature of the transfer plays a role which is often more depressing to cell proliferation than the addition of cancerolytic agents. Certainly, some excellent work in evaluating the effect of chemotherapeutic agents on tissue freshly explanted into culture has been reported by Biesele,<sup>7</sup> by Wright and associates,<sup>8</sup> and by

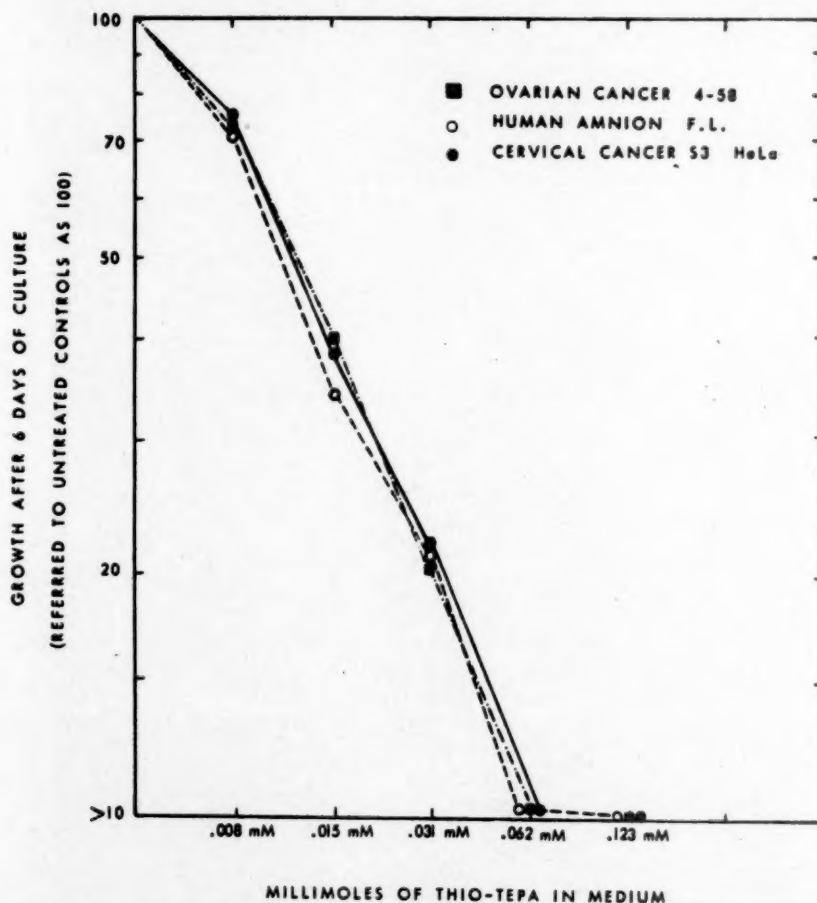


Fig. 10.—The cytotoxic effect after 6 days of thioTEPA on three human cell strains in vitro.

many others as listed by Pomerat and Leake.<sup>9</sup> These authors also emphasize the limitations of the method. Before the virologist could utilize tissue culture in clinical application, it was necessary to have well-established strains of cells growing in vitro. For the same reasons it seems necessary that the dependability and predictability of long-term cell cultures would be necessary in order to evaluate carcinolytic agents on a day-to-day clinical basis.

Long-term cell cultures present a most obvious inadequacy, however. Cell lines derived from entirely dissimilar tissues respond with almost identical susceptibility to a given chemotherapeutic agent. Eagle and Foley<sup>6</sup> previously reported this somewhat surprising observation and the data reported herein

stand in agreement. Indeed, various cell strains growing in long-term cultures develop common antigenic properties.<sup>10</sup> The effect on the cell growing in culture appears to be more characteristic of the carcinolytic compound than on the tissue from which the cell was cultured. It seems entirely possible that cells of different origin growing in culture under the same conditions through many transfers develop similar biochemical and biological characteristics and become more the product of culture conditions than of the tissue of origin. These changes are substantiated by reports of the "production" of malignant

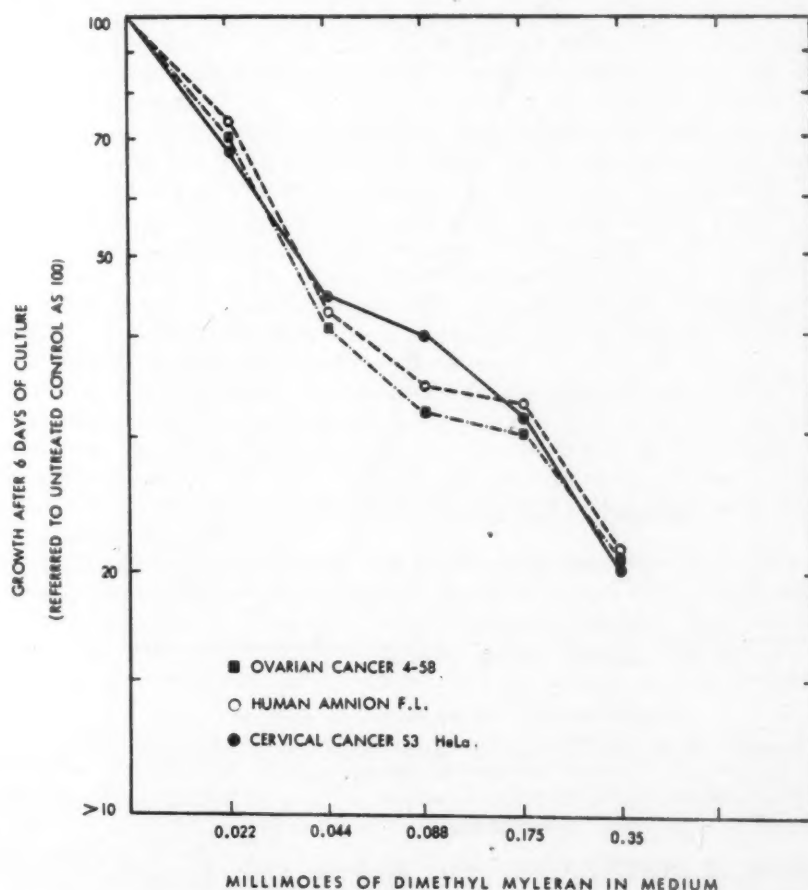


Fig. 11.—The cytotoxic effect after 6 days of dimethyl Myleran on three human cell strains in vitro.

changes in vitro and by progressive increases in cell chromosome counts as a strain passes through many transfers in culture. One must also consider that, except for the folic acid analogues, it is difficult to demonstrate a significant correlation between cytotoxicity of an agent in tissue culture and carcinolytic action in vivo, and between cytotoxicity in tissue culture and animal toxicity.

In spite of such serious inadequacies, tissue culture methods do provide a means of studying the effects of carcinolytic agents on cells under precisely controlled and easily observed conditions. The compounds studied here have been added to cultures in amounts which approach clinical application. The



results are reproducible and the effects of both the agent and the level of drug vary significantly. It seems likely, therefore, that by such methods basic information pertinent to the treatment of cancer will be obtained.

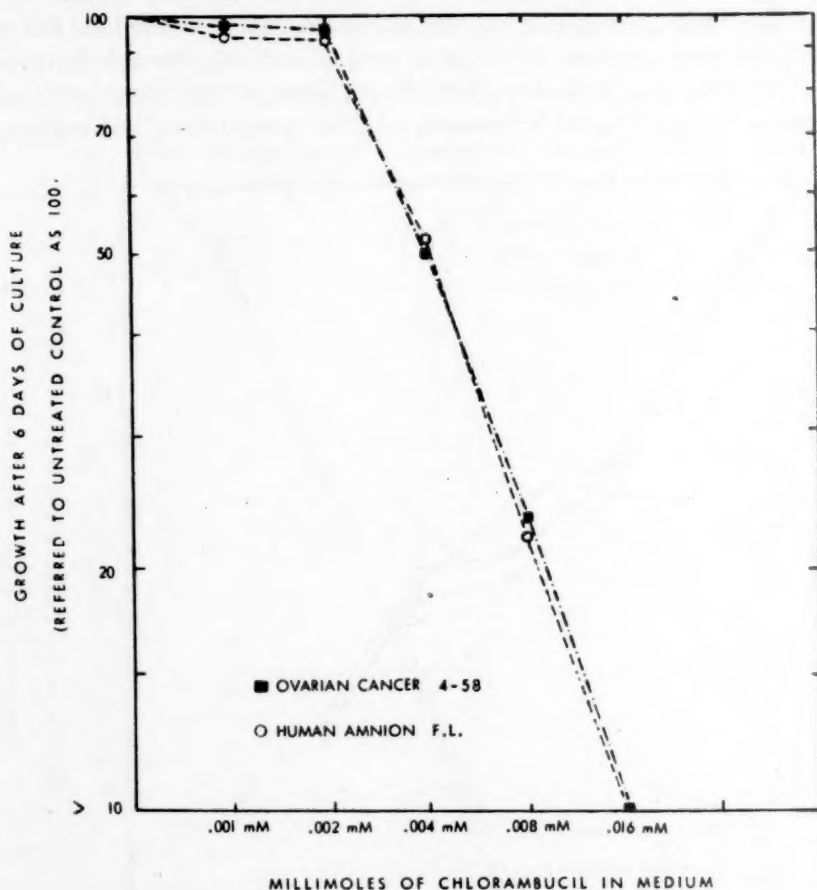


Fig. 12.—The cytotoxic effect after 6 days of chlorambucil on ovarian cancer cells (4-58) and Amnion F.L. cells.

### Summary

1. The effects of thioTEPA, dimethyl Myleran and chlorambucil on cell strains of cervical carcinoma, ovarian carcinoma, and normal amnion growing in tissue culture are noted.

2. The susceptibility of each of three cell strains to the cytotoxic effect of a given carcinolytic compound does not vary significantly.

3. The cytotoxic effect in tissue culture appears to be more characteristic of the chemotherapeutic compound than of the established cell strain or its tissue of origin.

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### Discussion

DR. GEORGE A. HAHN, Philadelphia, Pa.—It is apparent that there are basic differences in the chemical attack on human infections and the chemical attack on malignant disease. With infectious processes the efficient defense mechanisms of the body usually support the effect of the anti-infectious agent. In malignancy, however, no basic restorative defensive forces are at work since differences in cell structure are the disturbing factors.

Paraphrasing Woglom, "so slight is the difference between the cancer cell and its normal ancestor that it is almost—not quite, but almost—as hard as finding some agent that will dissolve away the left ear, say, yet leave the right ear unharmed."

In utilizing tissue cultures it seems likely that the original explants contain several lines of cells and that certain cells are better able to survive under test-tube conditions. It has been noted by other investigators that carcinomatous tissue from certain patients may grow better in tissue culture than malignant tissue taken from other patients irrespective of the pathological grade of the malignancy, the rate of growth of the tumor in the patient, or the freshness of the specimen.

Culture methods differ fundamentally from heterotransplants of tumors, with experimental animals as the hosts for the tumor. In this type of growth, genetic factors in the animal, age, sex, hormonal status, and the general health of the animal may significantly alter the response of the tumor to its tumor bed. Unusual defense reactions may develop against the foreign tissue which would not ordinarily take place with the formation of a spontaneous malignancy.

The tumor bed itself, which may be the most important single factor in the survival or demise of the tumor cells, of course, cannot be evaluated in culture methods.

The presence of a tumor in a host produces chemical and structural changes in tissues which do not contain malignant cells. Enzyme activity, nutrition, hormone balance, tissue structure may be altered and the animal may die because of widespread change.

In the evolution of chemical agents certain points stand out. Tumors originally responsive may become resistant, even though the susceptibility of the host remains unchanged. This resistance may be due to changes in the structure of the tumor itself or it may be that the chemical agent destroys all cells responsive to it, allowing resistant cells gradually to multiply.

Cancer treatment may be improved by the addition of other agents, changes in oxygen tension, hormonal status, or enzymatic elements. General supportive measures must be utilized and regional chemotherapy may play an important role.

Dr. Moore has stressed the practicability of human tissue culture as a means of assessing chemotherapeutic agents under precisely controlled and easily observed conditions. In the investigation presented today, Dr. Moore states that the cytotoxic effect, in culture, appears to be dependent on the chemical compound rather than the cell strain or its tissue of origin.

DR. JOHN A. WALL, Houston, Texas.—One of the basic problems in the surgical treatment of neoplasms is that, in the majority of patients in whom the local disease has been eradicated, death results from distant spread of cancer cells through the lymphatic and vascular channels and throughout the body cavities. It is also well known that a relatively small proportion of such cells released at the time of operation eventuate in metastatic growth. There are numerous reports showing that unestablished tumor foci are more susceptible to destruction than are larger tumors which have become well established.

Complete surgical excision of a tumor, followed by chemotherapy for the residual cells in the tumor bed, as well as those released into the general circulation, certainly seems to be a plausible approach.

Under the auspices of the Cancer Chemotherapy National Service Center of the National Cancer Institute, 27 university surgery departments and 21 surgery departments of the Veterans Administration Hospitals have developed a statistically controlled co-operative clinical study on the *systemic* use of chemotherapy in the surgical treatment of cancer. Two investigations are now under way. The first is using thioTEPA in resectable carcinoma of the stomach, and the second is using nitrogen mustard in resectable carcinoma of the lungs.

The selectivity of a therapeutic agent is exemplified by the use of radiophosphorus in neoplasms of the breast. This work first reported by Low-Beer and Bell of San Francisco has emphasized the practicability of this means of treatment.  $P^{32}$  has been the radioisotope of choice since phosphorus must be available for the cancer cell synthesis of nucleoprotein. Radioactive phosphorus can thus be directed to the neoplastic cell. This particular isotope has so far been used principally in breast and prostatic cancer.

DR. J. H. FERGUSON, Miami, Fla.—I was particularly interested in Dr. Moore's experience with thioTEPA because at the University of Miami I have treated 17 patients with carcinoma of the cervix with this agent. These were women with far-advanced carcinoma of the cervix who had received the limit of surgical or radiologic therapy and to whom we had nothing else to offer. I regret to report that we had uniformly poor results. The drug failed to halt the advance of the disease in any case. This was a particularly severe trial for the drug and I do not wish to imply that all possibilities of this agent have been exhausted. For example, I might now try a combination of surgery and the thioTEPA.

One woman I treated had a chain of enlarged nodes in the inguinal area which were proved to be metastases. The largest node was injected with thioTEPA and was later excised. No cancer tissue was left but it seems more likely that this was a simple chemical destruction of the malignancy rather than any specific cancerocidal effect.

I have also treated 8 patients with ovarian cancer with triethylene thiophosphoramide. Four of these patients have died and 4 are still under treatment. It is too early to offer an opinion on the effectiveness of this agent in the treatment of cancer of the ovary.

DR. MOORE (Closing).—Our clinical results with thioTEPA also have been far from enthusiastically accepted on our service and although the results have been better with ovarian carcinoma, palliatively speaking, than with cervical carcinoma, I do not think that the compound holds much hope for these two diseases.

Dr. Hahn asks if the clinical change that we see in the patients who are getting thioTEPA is due to the susceptibility of the cancer or to the resistance of the patient. I am sure that I cannot answer this question and I do not think anyone else can. It is interesting to speculate about it, and I am inclined to think that the resistance of the patient has as much to do with it as the susceptibility of the tumor.

Dr. Hahn also asks if we feel that the equality of results in the various strains occurs because of the long-term nature of the cultures and I feel relatively certain in my own mind that this is true. As a matter of fact, a recent report (Science 128: 198, 1958) indicated that in long-term cultures the various strains even develop identical antigenic properties and this observation indicates, I believe, that these cells, after a period of time become more a product of the culture conditions than of the original tissue of origin.

## LONGITUDINAL STUDIES OF GONADOTROPIN EXCRETION IN THE STEIN-LEVENTHAL SYNDROME\*†

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THE Stein-Leventhal syndrome, characterized by disturbed menstruation, hirsutism, and bilateral polycystic ovaries, is a rare, but well-established, clinical entity. Wedge resection, an empirical form of therapy, is often successful although the etiology of the syndrome remains obscure. Since ovulation, a process which requires that an FSH-primed follicle be stimulated by ICSH,‡ is suspended in this condition, a disturbance in the elaboration or release of the luteinizing hormone becomes a strong etiological possibility. Therefore, when a biological method for measuring the urinary excretion of ICSH was developed in our laboratory,<sup>1</sup> it seemed an ideal tool for the investigation of the patient with the Stein-Leventhal syndrome. It is the purpose of this paper to present a description of the pattern of ICSH excretion in patients with the polycystic ovary syndrome. The data were secured as a part of a larger study which dealt with ICSH excretion in normal adult women<sup>2</sup> and in patients with various diseases of the reproductive tract.<sup>3</sup>

In their original publication describing this syndrome,<sup>4</sup> Stein and Leventhal postulated that the ovarian pathology and the clinical picture were due to hypersecretion by the anterior lobe of the pituitary gland. They<sup>4,5</sup> founded their hypothesis on the observation that the administration of large doses of anterior lobe extracts to animals over long periods of time causes histological changes in the ovaries similar to those of the Stein-Leventhal syndrome, i.e., multiple follicle cysts with an inactive granulosa and an active theca interna, a thickened capsule, and fibrosis of the stroma.

Cytological evidence pertinent to Stein's hypothesis has been presented by Sommers and Wadman.<sup>6</sup> In a study of 26 women found at autopsy to have polycystic ovaries, seven pituitary glands were available for microscopic examination. The basophils, which are thought to elaborate the gonadotrophic

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‡In recent years, a number of investigators have come to doubt the independent existence of FSH and ICSH and have proposed an alternative unitarian hypothesis. However, we believe that the preponderance of evidence still favors the existence of two separate gonadotropic hormones, and have retained the traditional dualistic nomenclature.



hormones, tended to be aggregated in hyperplastic nodules. Moreover, they were found to constitute 31 per cent of the total number of cells as compared to 16.3 per cent in the controls. Although the level of activity of a gland cannot always be inferred from its histological appearance, the increased percentage of basophils in this instance is at least compatible with Stein's view.

TABLE I. PITUITARY GONADOTROPIN ASSAYS OF FSH

	YEAR	NO. CASES	METHOD	NORMAL	HIGH	LOW
Schneider and associates <sup>8</sup>	1947	10	Mouse uterine weight	7	3	0
Plate <sup>9</sup>	1951	3	Mouse uterine weight	0	0	3
Greenblatt <sup>10</sup>	1951	6	Mouse uterine weight	2	4	0
Du Toit <sup>11</sup>	1951	3	Mouse uterine weight	1	1	1
Buxton and van de Wiele <sup>12</sup>	1954	6	Mouse uterine weight	Not excessive		
Haas and Riley <sup>7</sup>	1955	7	Ovarian and uterine weight	5	1	1
Cervino and associates <sup>13</sup>	1956	2	Rat uterine weight	1	0	1
Ingersoll	1957	26*	Mouse uterine weight	22	3	1
Total		63		38	12	7

\*Includes 12 cases reported by Ingersoll and McDermott.<sup>16</sup>

TABLE II. PITUITARY GONADOTROPIN ASSAYS OF ICSH

	YEAR	NO. CASES	METHOD	NORMAL	HIGH	LOW
Cervino and associates <sup>13</sup>	1956	2	Seminal vesicle histology	2	0	0
Keettel and associates <sup>20</sup>	1957	10	Ovarian histology	0	10	0

Physiological evidence in support of the theory of hypersecretion of gonadotropin has also been sought. The level of urinary gonadotropin excretion has been studied by means of a variety of bioassay techniques. Except for Haas and Riley,<sup>7</sup> who made repeated determinations at intervals of one week, all investigators based their conclusions on the results of a single assay. The results of these spot determinations are summarized in Tables I and II. It will be noted that the assays have been divided into two categories, namely, those for FSH and ICSH. Although we have retained the author's classification, it must be pointed out that in many instances the mouse uterine weight method, which in all probability measures FSH plus ICSH, rather than FSH alone, was employed. Schneider and his associates<sup>8</sup> in a series of 14 patients with the Stein-Leventhal syndrome, 11 proved by operation, obtained normal values in 7 and high in 3 patients. Plate<sup>9</sup> found diminished FSH in a study of 3 hirsute patients with hyperthecosis, only one of whom seemed to have the typical Stein-Leventhal syndrome. Greenblatt<sup>10</sup> demonstrated moderately elevated levels in 4 Stein-Leventhal cases and normal levels in 2. Du Toit<sup>11</sup> did FSH assays on 7 hirsute patients, 3 of whom seem typical of those with the Stein-Leventhal syndrome. A normal FSH value was found in one, low in one, and high in one. In 6 patients, Buxton and van de Wiele<sup>12</sup> tested for excessive amounts with negative results. Haas and Riley found the excretion of urinary gonadotropins to be normal in 5, elevated in one, and depressed in one of 7 patients proved by operation to have the Stein-Leventhal syndrome. The data from Cervino and associates<sup>13</sup> report the unusual circumstance of the disease occurring in two sisters; the level was normal in one, low in the other. In a series of 26 patients, Ingersoll<sup>14</sup> found 22 to have normal, 3 elevated, and one depressed levels. In summary, approximately one-sixth of the assays yielded elevated values.

Other theories as to the etiology of this syndrome have been advanced. In 1937, Bailey,<sup>15</sup> impressed by the amenorrhea of a group of 17 patients

with polycystic ovaries, came to a conclusion diametrically opposed to that of Stein. He noted the lack of follicle ripening and ovulation, and suggested that it implied a deficiency rather than an excess of pituitary secretion. By 1950, additional knowledge had been gained concerning reproductive physiology, and Ingersoll and McDermott<sup>16</sup> suggested that the hyposecretion of gonadotropin postulated by Bailey might involve more specifically a deficiency of ICSH.

There are also good reasons for believing that there may be an excess of ICSH in this syndrome.<sup>16, 17</sup> A prominent microscopic feature of the polycystic ovary is hypertrophy and luteinization of the theca interna. Since the theca is a primary target of ICSH stimulation,<sup>18</sup> its hypertrophy is regarded by Plate<sup>9</sup> as an argument for the concept that there is hypersecretion of ICSH in the Stein-Leventhal syndrome. The preliminary excretion patterns showing abnormally frequent elevations of ICSH which we<sup>19</sup> presented to the Endocrine Society in 1955 constituted physiological evidence in support of this theory.

In Table II are summarized the results obtained by two subsequent investigators who have studied ICSH excretion. The methods which were employed in these studies and in our own investigation are thought to be relatively specific for ICSH. Cervino and co-workers<sup>13</sup> employed a count of the mitotic figures in the seminal vesicles and prostate to measure the ICSH effect in two sisters, and found normal levels in both. Using the histological response of the immature rat ovary as the physiological indicator, Keettel and associates<sup>20</sup> demonstrated an excess of ICSH in 10 of 11 patients with polycystic ovaries. Except for the study of Keettel and co-workers, in which the presence of an elevated level of ICSH was a primary criterion for the selection of cases, Tables I and II reveal precisely that scattering of normal, high, and low values which might have been predicted.

In patients with the Stein-Leventhal syndrome, ovarian-pituitary reciprocity, though disturbed, is not wholly destroyed. These patients menstruate at intervals, ovulate occasionally, and have even been known to conceive. Some semblance of rhythmic gonadotropin secretion must be present for these phenomena to be possible. In normal women, spot determinations necessarily yield a scattering of high, low, and normal levels, since the gonadotropic hormones are known to be released in a cyclic manner. Therefore, to achieve a clear differentiation between the patient with the Stein-Leventhal syndrome and the normal woman, it seemed essential to perform serial assays over comparatively long periods of time. The biological technique which we have employed depends upon androgen production in response to ICSH stimulation of the Leydig cells of the hypophysectomized immature male rat. Since FSH does not potentiate ICSH in this action, its presence in unfractionated urinary extracts presumably does not interfere with the assay. The ventral lobe of the prostate is a convenient and sensitive indicator of the amount of androgen secreted by the interstitial cells.

### Material

To date, we have been able to accumulate data on 6 patients with the Stein-Leventhal syndrome who have been studied over periods of from 28 to 122 days. The relevant clinical information concerning these patients is summarized in Table III. All of them gave an abnormal menstrual history; in the married patients, infertility was the primary complaint. Enlargement of the ovaries was demonstrable in every case; physical examination was otherwise not remarkable except for hirsutism in 50 per cent of the patients. 17-Ketosteroid

TABLE III. CLINICAL DATA ON 6 STEIN-LEVENTHAL PATIENTS

PATIENT	AGE	MARITAL STATUS	COMMENT	17-KETOSTEROIDS (MG./24 HR.)	BASAL BODY TEMPERATURE CHART	ENDOMETRIAL BIOPSY
H. P.	26	Single	Classical history and physical examination; hirsute; culdoscopy shows typical polycystic ovaries; operation contemplated	13.1	Monophasic	Proliferative
A. B.	25	Married 2 years	Sterility; hirsutism; oligomenorrhea, enlarged ovaries; operation declined pro tem.	9.2	Monophasic	Hyperplasia
D. E.	24	Married 4 years	Sterility, oligomenorrhea; pregnancy following wedge resection	10.2	Monophasic	Proliferative
E. K.	29	Married 5 years	Sterility; anovulatory preoperatively; ovulatory menstruation and pregnancy after wedge resection	11.0	Monophasic	Proliferative
M. B.	26	Single	Oligomenorrhea; no hirsutism; ovulatory menstruation after wedge resection	17.0	Monophasic	Hyperplasia
V. H.	24	Married 2 years	Hirsute; amenorrhea preoperatively; postoperatively occasional ovulatory menses without pregnancy after previous wedge resection	8.0	Monophasic	Proliferative

levels were normal, endometrial biopsies were proliferative in character, and the basal body temperature patterns were monophasic in all instances. In 4 patients the diagnosis was confirmed by operation and in one by culdoscopy. One patient has declined operation so far, although her history, physical findings, and laboratory results are classical. Postoperatively, 2 of the 3 married patients achieved a pregnancy; one ovulates occasionally but has failed to conceive. The single patient ovulated immediately after the operation but has gradually reverted to an anovulatory state.

### Methods

Each patient collected all of her urine in serial 24-hour specimens and kept a continuous record of her basal body temperature. As a check against gross errors of collection, the urinary creatinine was determined. A single

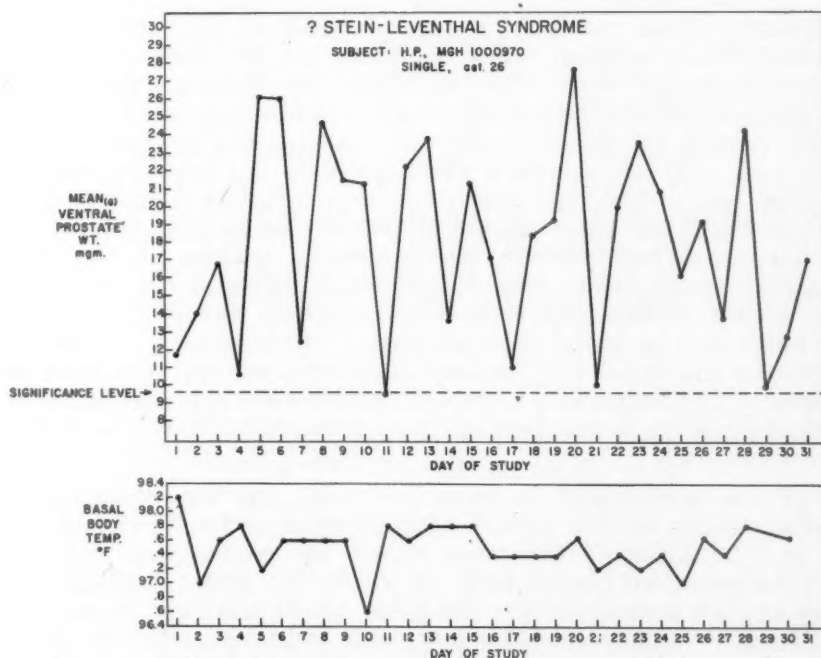


Fig. 1.—Changes in ventral prostate weight induced by urinary extracts from H. P., a 26-year-old single woman with the Stein-Leventhal syndrome. In this and the two subsequent figures the geometric mean weights are plotted on a logarithmic scale.

dose assay for ICSH was performed in order to obtain a qualitative description of the excretory pattern which could be compared with that obtained in normal women. An 18-hour aliquot of the 24-hour specimen was concentrated by means of kaolin adsorption and the equivalent of 6 hours of urine injected into each of 3 hypophysectomized male rats, according to a method previously described.<sup>21</sup> The testis weights of the animals were also recorded as an index of FSH excretion. Since it appears that the specificity of this method for measuring FSH is inferior to that employed for ICSH, the results are more difficult to interpret. They are reported in detail elsewhere.<sup>2</sup> The remaining 6-hour aliquot of urine was used for the determination of pregnanediol content by a modification of the method of Astwood and Jones.<sup>22</sup> In most instances, spot determinations only were done to determine the presence or absence of pregnanediol. Endometrial biopsies were secured in some instances during the first 24 hours of flow which marked the end of a collection period.



### Results

A representative example of the preoperative excretion pattern of ICSH is shown in Fig. 1. This 26-year-old single woman was studied over a period of 31 days. The excretory curve is shown in the upper half of the figure and the concomitant basal body temperature in the lower half. The days of study are indicated on the abscissa, and the geometric mean prostate weights on the ordinate. The "significance level" indicates that geometric mean weight at or above which the prostate weights of the test animals, based on data from three rats, may be regarded as differing significantly ( $p=0.025$ ) from those of the control animals. It will be noted that there are marked fluctuations of the level of excretion of ICSH, that the interval between the peaks is variable, and that no definite trend can be identified during this 31 day study. The individual excretion patterns of the other 4 patients studied preoperatively are similar in every respect.

The abnormality of the excretory pattern of ICSH in the Stein-Leventhal syndrome is immediately evident when compared to the excretory pattern during a normal menstrual cycle. Two examples, one from a short and one from a long cycle, are taken from a study of 17 normal cycles in 13 volunteers. In Fig. 2 which depicts the shorter cycle, two features will be noted: (1) a sharp midcycle peak of ICSH excretion which precedes the luteal rise in basal body temperature, and which continues for approximately 7 days; (2) a secondary rise in ICSH of lesser magnitude which occurs just prior to the onset of the next menstrual period. The excretory pattern of the longer cycle, that of a 33-year-old woman with 5 children, is shown in Fig. 3. In this cycle there are prominent fluctuations in ICSH excretion during the follicular phase, one of which will be noted to occur during menstruation. A midcycle peak again precedes the luteal rise in basal body temperature; the level continues to be elevated for a total of 4 days. Although there is a suggestion of a secondary peak during the latter part of the luteal phase, it is less striking than in the previous cycle.

In Table IV are summarized the geometric mean prostate weights of the entire series of specimens studied in each of the 6 cases of the Stein-Leventhal syndrome, as well as the composite mean values for normally menstruating women and for the untreated control rats. It will be noted that in the 5 Stein-Leventhal cases studied preoperatively, the mean prostate weight in every instance is significantly higher than the composite value obtained in normal women. In the 2 patients (M. B. and V. H.) who were studied postoperatively, the excretion of ICSH approaches normal levels.

TABLE IV. THE MEAN (GEOMETRIC) VENTRAL PROSTATE WEIGHTS (ANTILOGARITHMS) OF RATS INJECTED WITH URINARY EXTRACTS

PATIENT	NO. OF CONSECUTIVE DAYS STUDIED	GEOMETRIC MEAN VENTRAL PROSTATE WEIGHT (ANTILOG. MLVPW) (MG.)
H. P.    ? Stein-Leventhal syndrome (preop.)	31	17.1
A. B.    ? Stein-Leventhal syndrome (preop.)	30	20.8
D. E.    Stein-Leventhal syndrome (preop.)	28	20.3
E. K.    Stein-Leventhal syndrome (preop.)	36	22.1
M. B.    Stein-Leventhal syndrome (preop.)	30	23.4
	(postop.)	16.0
V. H.    Stein-Leventhal syndrome (postop.)	122	11.8
13 normal women throughout 17 menstrual cycles	463	13.8
Untreated control rats		7.2

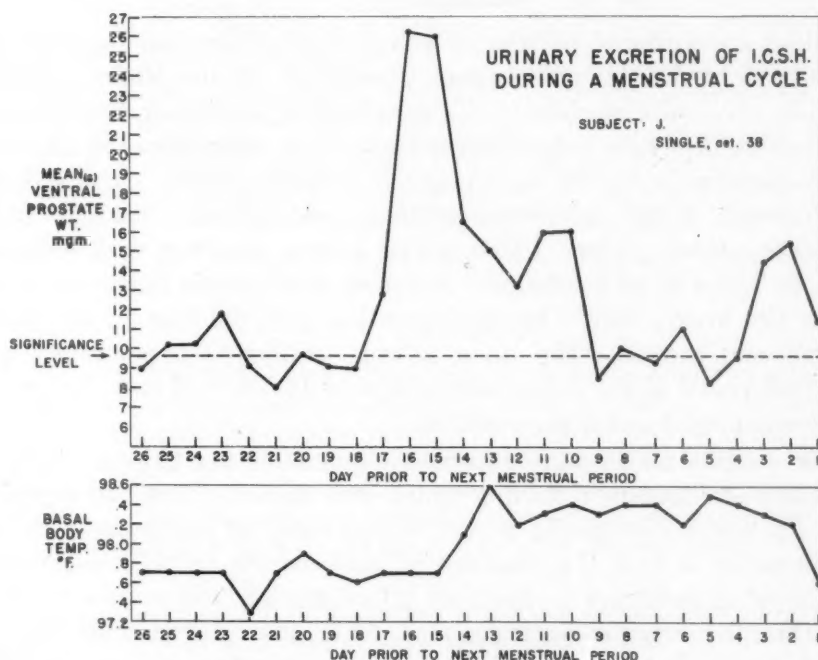


Fig. 2.—Changes in ventral prostate weight induced by urinary extracts from J., a 38-year-old single woman with a 26 day menstrual cycle.

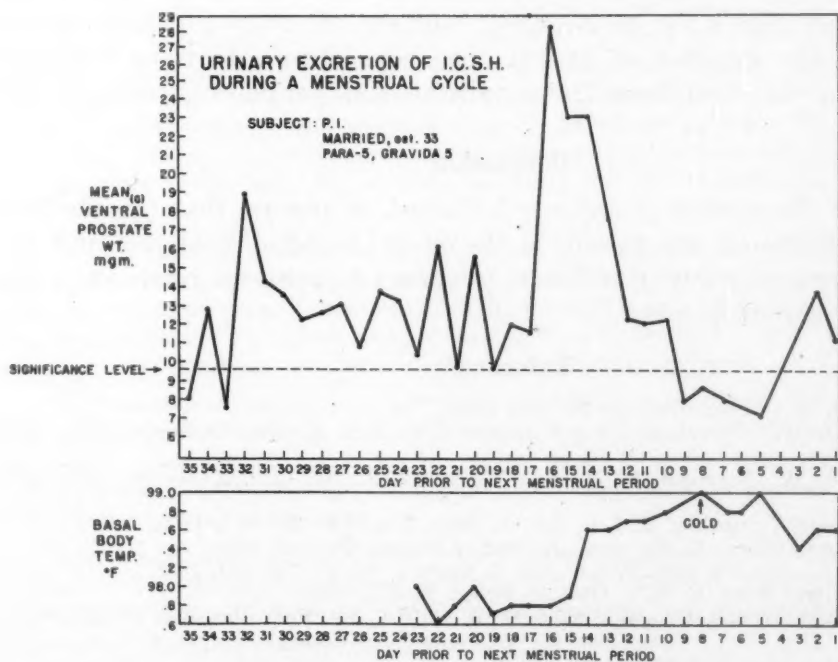


Fig. 3.—Changes in ventral prostate weight induced by urinary extracts from P. I., a 33-year-old para v with a 35 day menstrual cycle.

### Comment

In revealing a disordered pattern of gonadotropin excretion these studies shed additional light on the pathological physiology of the Stein-Leventhal syndrome. The classical experiments in reproductive physiology have demonstrated that ovulation occurs only when gonadotropic stimulation of adequate intensity and duration is applied to a properly primed follicle. In the Stein-Leventhal syndrome, ICSH may occasionally be released in a manner which approximates the normal pattern. This seldom occurs, however, with sufficient exactitude to be followed by ovulation. Frequent and erratic bursts of ICSH impinge upon the ovary, which becomes crowded with follicles in all stages of development and atresia. The theca interna undergoes hypertrophy and luteinization as a result of the cumulative action of ICSH, and may ultimately constitute a mechanical barrier to ovulation.

The testis weights which were recorded along with the prostate weights exhibited parallel oscillations, a finding which may indicate that the secretion of FSH also fluctuates abnormally in the Stein-Leventhal syndrome. An alternative explanation is that the response of both organs actually constitutes a measure of total gonadotropin. Such an interpretation will appeal to those who believe that the original separation of FSH from ICSH represents a chemical artifact and that, in reality, the pituitary secretes only one gonadotropic hormone.

Since this study was begun, the controversy regarding the unity or duality of the pituitary gonadotropins has increased in intensity. Regardless of the outcome (which cannot yet be foreseen), however, the results of these studies indicate that the excretion of at least one gonadotropic hormone fluctuates abnormally in the Stein-Leventhal syndrome and periodically reaches high levels.

### Conclusion

Although the number of patients is limited, it appears that (1) the level of excretion fluctuates abnormally in the Stein-Leventhal syndrome and (2) high levels are attained with sufficient frequency to raise the composite value above that of normal women.

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### Discussion

DR. W. C. KEETTEL, Iowa City, Iowa.—The important contributions of this paper are the verification of the excessive production of ICSH, the marked daily fluctuations in the polycystic ovary syndrome, and the elevation of ICSH excretion at midcycle during normal menstruation. The methods and conclusions of this paper seem valid. I would like to ask the essayist to describe in more detail the hormone findings after wedge resection. Do they show the wide daily fluctuations and elevated levels or are they comparable to the findings of a normal menstrual cycle? Are the postoperative hormone changes of prognostic significance?

We have not studied the LH excretion during the normal menstrual cycle, so we cannot compare our methods with those of the essayist in this group. However, we have studied the gonadotrophin excretion in patients with the polycystic ovary syndrome and the young women with amenorrhea due to other causes.

In 1956 we presented our method of selection of patients with the polycystic ovary syndrome by the presence of LH in the urine and the patient's ovarian response to sheep pituitary FSH. Since that time 11 additional patients have been studied. While we have not obtained daily hormone levels, many patients had from 5 to 8 determinations prior to operation. Of the 24 patients, 21 had urinary gonadotrophic studies. There were 57 specimens showing LH, 7 specimens showing FSH, and 11 were reported in the normal range. Table I compares the gonadotrophin findings in 38 young patients with other types of amenorrhea. In this group the predominant hormone findings were either normal or FSH in type. Only 16 specimens showed the presence of LH. This corresponds with Dr. Ingersoll's findings.

It is interesting to note that in this group of young patients with various types of amenorrhea, 10 had gonadotrophins which were consistently elevated to castrate levels. We found several other patients who showed wide fluctuations in gonadotrophins ranging from normal to castrate levels. The 6 patients showing the presence of LH on at least one occasion did not manifest findings suggestive of the Stein-Leventhal syndrome.

The response of our patients with polycystic ovaries to exogenous FSH stimulation has been a very consistent finding, as 22 out of our 24 patients showed marked enlargement of the ovaries. Only one of our 36 normal control patients showed a comparable ovarian response. Recently, 4 patients with amenorrhea, but not excreting LH consistently, were given FSH without ovarian enlargement.

Our present series and the author's cases indicate a rather consistent excretion of LH in patients with the polycystic ovary syndrome. It is difficult to know whether this is of etiological significance. However, normal patients, or other patients with secondary amenorrhea, do not show this characteristic pattern of LH secretion.

It appears that the Stein-Leventhal syndrome represents a wide variety of symptoms. Should patients have the diagnosis of this entity on the basis of clinical symptoms, pelvic findings, ovarian histologic changes, hormonal findings, or ovarian response to FSH therapy?



Are the histologic changes characteristic or are they present in other situations? Perhaps the typical textbook findings may represent the final phase of the syndrome, which is not as easily corrected.

It is hoped by such investigations that eventually the exact etiology of this syndrome will be determined. This may transfer the treatment of this disease complex from a surgical to a medical management.

TABLE I. GONADOTROPHIC ASSAYS IN PATIENTS WITH AMENORRHEA, AGED 17 TO 30

	NO. OF PATIENTS	LH	FSH	NORMAL
Polycystic ovary syndrome	21	57	7	11
Other types of amenorrhea	38	16	42	41

DR. D. N. DANFORTH, Chicago, Ill.—Dr. Stein and Dr. Leventhal together have made two very significant contributions. The first was their description of the syndrome which bears their name. The second was that through this description they provided countless workers with many fascinating hours of speculation and stimulated the most prodigious effort to explain and treat specifically the various aspects of this problem. Now, some 20 years later, only four unanswered questions remain: these are its cause, a specific nonsurgical means by which it may be diagnosed, a direct and uniformly successful means of treating it, and a proper explanation as to why successfully treated cases have responded in a favorable manner. But this is not to say that no progress is being made, for the relationships in this problem are of the greatest complexity, the required assays are often indirect and their end point is not sharp, and much manipulation and interpretation of the data are necessary before one may make a final conclusion as to significance. So it is that each new facet of information brings us one step closer. It is in this particular way that Dr. Ingersoll's paper is of significance, since it does shed light on at least one of the unsolved riddles of this disease. Certainly it is not possible to make sweeping conclusions, but these data suggest that in the Stein-Leventhal syndrome the excretion levels of interstitial-cell-stimulating hormone, and possibly also of FSH, are increased, and fluctuate in a sharp and bizarre manner from day to day, in contradistinction to the levels in the normally menstruating woman. It is entirely possible that such studies may provide a proper diagnostic tool for this problem. Also, it will be evident that spot determinations of gonadotrophic hormones, and possibly others as well, may give an entirely spurious picture when considered against day-to-day determinations.

As we contemplate these results, it is interesting to speculate as to the manner in which they may be interpreted as an aid in the explanation of the Stein-Leventhal syndrome. Certainly if the FSH levels do parallel the ICSH levels, this finding, in addition to its potential value as a diagnostic tool, will also provide support for the thesis that the primary defect is one of pituitary hypersecretion.

In the evaluations of these results, it would be extremely helpful if Dr. Ingersoll would point out specifically the factors in the procedure or the data which caused him to present the results in terms of the geometric means. Also, granted that this statistical technique is in this particular case more illuminating than others, I should be interested to know the range of normal which permits the conclusion that the variations presented are significantly different from normal values.

DR. INGERSOLL (Closing).—I wish to thank Dr. Keettel and Dr. Danforth for their discussions. Their questions give me an opportunity to acknowledge the industry and the ability of my co-author, Dr. Janet W. McArthur, who is responsible for much of this work.

In reply to Dr. Keettel's question in regard to what have been the hormone findings after wedge resection, we have studied only 2 patients postoperatively. I have a slide of one of those patients—a single woman 26 years of age. On this slide the geometric mean prostatic weights are shown above and the basal body temperatures below. The first part of

the slide depicts the excretion levels preoperatively during a 29 day collection interval; multiple peaks of ICSH excretion occur which are similar to the pattern shown in Fig. 1, H. P., and are characteristic of the pattern seen in the Stein-Leventhal syndrome. The second part of the slide shows the excretion curves after wedge resection. During this 31 day collection interval one peak of ICSH excretion occurred which preceded the rise in basal body temperature by 24 hours and was followed by menstruation in 14 days shown to be ovulatory by the basal body temperature chart and pregnanediol excretion. In this one instance the postoperative excretion curve of ICSH is quite similar to the normal pattern of ICSH excretion as illustrated in Figs. 2 and 3.

The other patient whom we studied postoperatively collected urine for 122 consecutive days. At the close of this interval she ovulated, at which time the excretory curve of ICSH resembled the normal pattern. During the early part of this 4 month interval there were frequent bursts of ICSH excretion with multiple peaks, but the ovary failed to respond. In these 2 cases the composite level approaches the values for normally menstruating women. The need for study of additional cases both pre- and postoperatively is obvious.

I was glad to see Dr. Keettel's figures on LH excretion of patients with amenorrhea of other etiology. We, too, have found that some of our patients with psychogenic amenorrhea have low levels of ICSH. He is to be commended for using multiple hormone assays on the same patient. In order to make the diagnosis of the Stein-Leventhal syndrome, the patient's history, physical examination, laboratory tests, and hormone assays must all be taken into consideration. The most important single factor in the diagnosis is the demonstration of bilateral enlargement of the ovaries; we use the culdoscope to help us in this regard. One of the disputed and unanswered questions is whether or not wedge resection of normal-sized ovaries in anovulatory patients is indicated or beneficial.

In reply to Dr. Danforth's question I am glad of the opportunity to explain why, in this study, the geometric mean of the observation (or the mean of the logarithms) has been employed in preference to the arithmetic mean. Perhaps because it requires some additional labor, logarithmic transformation of the response metameter is less frequently employed than it deserves to be.

As Moore and associates have pointed out, many of the chemical and physical processes involved in biological phenomena—such as the law of mass action, the relation of temperature to velocity of reaction, etc.—are such that an arithmetic change in a cause makes a geometric change in an effect. Indeed, it is difficult to find biologically important chemical, physical, or physicochemical processes where the relation between cause and effect is a simple, arithmetic function.

In consequence, the logarithms of biological data of this kind are more likely to be normally distributed than the data themselves and a logarithmic scale may be expected to represent the data, their mean, and their variation more faithfully than the arithmetic scale. The use of logarithms reduces the variability and prevents aberrant large values from exerting any undue influence on the results.

For all these reasons, such authorities as Moore and Gaddum recommend that in dealing with biological data of the type we have presented preference be given to a logarithmic transformation as a matter of course.

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## ATYPICAL PELVIC PAIN IN WOMEN: GYNECOLOGIC-PSYCHIATRIC CONSIDERATIONS\*

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THE woman who bitterly complains of persistent, bizarre pelvic pain out of proportion to the physical findings is the *bête noir* of the gynecologist. This physician is often baffled regarding the true diagnosis, and his plan of investigation and treatment all too frequently includes one or more medical and surgical misadventures. Fortunately, in recent years, physicians have evinced a greater concern over the possible emotional etiology and personality correlates of pelvic distress.<sup>1, 2, 3</sup> To further this interest, we have studied a group of 35 women with chronic functional pelvic pain from the gynecologic and psychiatric points of view.

### Review of the Literature on Functional Pelvic Pain

*Historical Aspects.*—The uterus has been implicated in personality disorders for many centuries. As Cohen and his associates<sup>2</sup> stated, "Hysteria was described in antiquity as a disease of women, and the disordered uterus was considered by Hippocrates, Galen, Aretaeus, and Celsius to be the source of this illness and its symptoms." Much later, Freud, Breuer, Charcot, and Bernheim<sup>4</sup> also considered the womb in the etiology of hysteria. Even today, one finds that attention is still focused upon the relationship between personality disorders, the uterus, and atypical or functional pelvic pain.

Giffin,<sup>1</sup> in an interesting theoretical consideration of the psychosomatic aspects of gynecology, makes reference to a provocative quotation describing the pitfalls of poorly focused therapy by T. Clifford Allbutt<sup>5</sup> in 1884: "... A neurologic woman seems thus to be peculiarly unfortunate. However bitter and repeated may be her visceral neuralgias, she is told either that she is hysterical or that it is all uterus. In the first place, she is comparatively fortunate, for she is only slighted; in the second case, she is entangled in the net of the gynecologist, who finds her uterus, like her nose, is a little to one side, or again, like that organ, is running a little, or is as flabby as her biceps, so that the unhappy viscus is impaled upon a stem, or perched upon a prop, or is painted with carbolic acid every week. Arraign the uterus and you fix in the woman the arrow of hypochondria, it may be for life." Giffin goes on to say, "To expect other in behavior than a woman is able to achieve is to bring defeat to

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both the patient and the pursuit of medicine—the woman condemned as ‘an old neurotic’ behaves in a fashion warranting the label only because of necessity—it is the responsibility of medicine to help her find a more satisfactory solution.”

Duncan and Taylor<sup>3</sup> referred to a number of interesting designations which have been applied to what they termed the “pelvic congestion syndrome” in years past. Their bibliography on this disorder, which includes aspects of functional pelvic pain, dates back to an 1858 article and to a German paper published in 1906 describing this disorder. Thus, concern has developed over the years regarding the tense, anxious woman who complains of pelvic discomfort and other related difficulties, the basis for which involves little or no organic disease.

*Recent Clinical Research.*—Lock and Donnelly<sup>6</sup> reported in 1947 upon the incidence of “psychosomatic disease” in gynecology patients who were referred to them privately over a 5 year period. Unusual pain was reported by many of these women. The total was divided into three groups as follows:

Group I, 1,191 patients with symptoms commensurate with the pathological findings.

Group II, 220 patients with symptoms in excess of the physical findings.

Group III, 348 patients with numerous symptoms unaccounted for by the physical findings.

Thus, approximately 33 per cent (568 patients, Groups II and III) of all patients showed signs of “psychosomatic illness,” according to these authors. They concluded that ignorance and fear appear to be the most important contributory factors in such disturbances which occur most frequently in association with childbearing and marital activities. Neither age nor occupation was found to be significantly different in the three groups, although Groups II and III tended to report more operations than did Group I. Notably, only 25 per cent of Group III patients were willing to accept referral for psychiatric help.

After tabulating impressions gleaned from 2 years’ work in a clinic for the assessment and treatment of psychological factors in gynecology patients, two British authors, Snaith and Ridley,<sup>7</sup> concluded in 1948 that 46 per cent of the patients in their series possessed “psychologically unstable constitutions.” Pain was a prominent complaint in these women also. Data were collected from interviews with patients and their families. These investigators logically concluded, “It seems justifiable to include a psychiatrist and a psychiatric social worker in every gynecology team.”

Taylor<sup>8</sup> in 1949 reported upon the clinical and theoretical aspects of pelvic pain based upon a postulated vascular disorder, pelvic congestion. Duncan and Taylor<sup>3</sup> in 1952 summarized their predominant findings in 36 patients with pelvic congestion as follows: (1) As a rule, these women had no secure family life in childhood after which to pattern their own lives. (2) There was no satisfactory relationship with a suitable mother with whom to identify. (3) These patients were usually unable to function adequately as women, either sexually or maternally. (4) They revealed signs of immaturity and dependent needs. (5) “Stressful life situations” prevailed in many cases. (6) There occurred an increase in blood flow in the vaginal walls during periods of tension, particularly in relation to resentment aroused by discussion of problems regarding husbands and children.

It has been the impression of other investigators that many women who complain of pelvic pain for which no medical basis is found can be classified as hysteric. In this connection, a study by Purtell, Robins, and Cohen<sup>9</sup> in 1951



concerning the clinical aspects of hysteria is worthy of attention. These workers included 50 hysteric women and 156 control subjects in their study. A list of 42 symptoms indicating the incidence of each in 50 hysteric women and 50 healthy controls was developed. The frequency of symptoms claimed by each patient ranged in number from 11 to 35 (mean 23) for the hysteric patients, as compared to a range of 0 to 13 (mean 4) in the healthy controls. As a rule, the hysteric women, compared to the controls, reported significantly more operations, a greater number of hospitalizations, and more marital difficulties—including dyspareunia. They were vague in describing their symptoms, presented nonspecific or multiple chief complaints, and were more dramatic, overtalkative, and overfriendly in their manner.

Cohen and associates<sup>2</sup> in a second study of 50 hysteric patients and 190 controls in 1953 reported a statistical comparison which further showed that hysteric women undergo an excessive number of surgical procedures (mean number of operations 3.8) as compared with healthy control patients (mean number of operations 1.9). Gynecologic operations were found to be especially frequent in hysteric patients. These had occurred seven times as often in such patients as in control subjects.

*Psychological Tests.*—In each of the studies just described, little use was made of objective tests or assessment instruments in studying the personality characteristics of patients with pelvic pain of unknown origin. Certainly, few have been reported in the literature. A notable exception is the 1956 study of Gidro-Frank and Gordon.<sup>10</sup> They used a simple "projection" psychological test. (Each patient was asked to make a drawing of a human being.) These investigators reported that a group of 32 women with chronic or intermittent pelvic pain revealed signs of immaturity and a denial of sexual differences in their drawings of the human figure. Similar findings did not appear in their control group of 25 unselected pregnant women.

*Theoretical Approaches.*—The most prominent work during the last decade on functional pelvic pain has been that of Howard C. Taylor, Jr., and his associates.<sup>3, 8, 11, 12</sup> Taylor maintains that the major factor in this disorder is an alteration in local circulation and fluid distribution. He<sup>3</sup> settled upon the term "pelvic congestion" in 1952 to describe this ailment.

Duncan and Taylor<sup>3</sup> summarized their analysis by saying, "On the basis of such observations, it has been proposed that pelvic congestion be considered one of the 'stress diseases,' representing a bodily reaction to stressful life experiences." They were able to demonstrate circulatory changes in the vaginal walls incident to discussions of their patients' personal problems. Greater hyperemia was associated with resentment, they observed. Two years later, Taylor<sup>11</sup> summarized the terminology and implied physiology relative to their pelvic syndrome as shown in Table I.

TABLE I. TERMINOLOGY AND IMPLIED PATHOLOGY IN THE PELVIC AUTONOMIC SYNDROME (AFTER TAYLOR<sup>11</sup>)

Inflammation	Chronic parametritis
Musculature	Spastische parametropathie
Sensory nerves	Grande néuralgie pelvienne
	Plexalgie hypogastrique
	Broad ligament neuritis
Vascular system	Congestion pelvienne
	"Congestion-fibrosis" syndrome
General autonomic disorders	Pelvipathia vegetativa
	Endosympathoses génitales
	Pelvic sympathetic syndrome

Taylor has certainly made noteworthy contributions toward defining many of the clinical phenomena associated with pelvic congestion. He has not concerned himself to any degree with specific personality or psychiatric characteristics of this type of patient, however. One gets the impression that at times Taylor even looks with some skepticism upon attempts to relate the occurrence of functional pain with psychiatric phenomena. As an example, in 1954 he<sup>11</sup> wrote, "The view has been expressed [by Cohen and his associates] that these pelvic complaints may be entirely psychiatric, hysterical manifestations, apparently without somatic components, imagined pains restricted to the mind of the patient." Yet, in the same article, he seems to agree with Cohen and his co-workers when he states, "As a result of the examination of clinical aspects, this syndrome appears most likely to be a disorder of the pelvic autonomic nervous system occurring in psychiatrically predisposed individuals as a result of stress of some kind." Despite this paradox, the reader is left with the conclusion that these patients do present basic emotional problems.

In view of the fact that psychiatric consultation has been utilized by Taylor and his group when major surgery has been considered for patients with pelvic pain, it is of interest and value to know more about the common personality or psychiatric characteristics which he and his collaborators found in such cases. Taylor is apparently satisfied, however, that the results reported by Duncan and himself<sup>3</sup> in 1952 are sufficient in terms of the psychiatric aspects of his patients. As noted previously, they did indicate that these women were immature, had insecure childhoods, diminished sexual drives, and were often frigid. In addition, stressful life situations were notable in many of their cases.

Hunter<sup>13</sup> in 1947 utilized the interesting concept of sensory conditioning to form the basis for the process by which a person neurotically develops complaints of pain through misinterpretation of sensory perception. Anticipation, fear, and sensory conditioning can often constitute the explanatory factors in nonorganogenic pain, he contended. This author makes reference to the experimental situation in which a college student who had been subjected to repeatedly painful electrical stimuli continued to give a pain reaction after the two hundredth application, although the final stimulus was only feigned. In much the same way, women patients come to associate "internal findings" with some of the facts, feelings, and ideas collected from the external world. Thus, both acceptable and unacceptable impressions become integrated with various specific sensory impulses. These, we are told, give rise to agreeable and disagreeable sensations and reactions to them.

Along much the same line, Giffin<sup>1</sup> discussed the role of implanted superstitions, fear, anxiety, personality type, emotional conflict, worry, and depression in the causation and/or exacerbation of menstrual disorders, dyspareunia, vaginismus, severe frigidity, pelvic pain, and menopausal difficulties.

*Conclusions from Survey of Literature.*—As one reviews key studies on this topic, it becomes clear that emotional and other personality factors have long been considered to play major roles in the development, diagnosis, and disposition of such cases. There appears to be general agreement among investigators that some type of emotional disorder is often involved in the problem of functional pelvic pain.

### Procedure

Although the principal physician is the logical person to institute the necessary psychological investigation as well as the pelvic evaluation and treatment, he frequently lacks the specific training and adequate time to pursue the psychological problem to its logical conclusion. It is reasonable, therefore, to institute an interdisciplinary approach in these cases of unusual pelvic pain.

Recognizing this need, we have developed a "clinic within a clinic" which includes a psychiatrist, a psychologist, and a gynecologist, who combine their efforts toward a proper interpretation and treatment of the patient's illness. The cases to be described here are the result of 3 years' experience with such a psychogynecologic approach to the patient with functional pelvic pain.

### Case Material

This is a study of 35 women with chronic disabling pelvic distress who presented essentially normal physical findings. They were selected over a 3 year period and were submitted to intensive medical and psychiatric study and therapy on a gynecologic outpatient service without referral to numerous ad hoc clinics. These were not sequential cases of unexplained pelvic pain, but they were chosen as definite and striking examples of this problem. Numerous mild or borderline cases were eliminated in favor of the more obvious ones for the sake of emphasis. Later, a statistical representation may be possible.

Our presentation of these patients will include a personality profile or vignette of certain individual types with comments regarding their background and the setting in which their difficulties began. The success and failure of general supportive therapy, as well as short-term psychotherapy, should likewise be of interest. Finally, we shall attempt a clarification of the dynamics of the problem of chronic functional pelvic pain in the psychoneurotic individuals studied.

*Age Incidence.*—The ages of our 35 patients were 20 to 42 years, the average being 32 years. The great majority of this group was in the decades of the twenties and thirties.

Although hysterectomy and/or partial oophorectomy had been accomplished in certain of these patients, no individual was found to be menopausal, despite vasomotor hyperactivity and menstrual aberration.

*Marital Status.*—Of the 35 patients, only one was single and but 2 were divorced. The marital history data suggest that the 34 married women had no initial fear of matrimony as indicated by the unusually early age at their first marriage. The fact is, most of them married early (and some more than once), with the average age at first marriage being 17 years. One was wed at age 13; 3 at 14; 2 at 15; 4 at 16; 4 at 17; 8 at 18; and one at 20 years of age. The oldest when married was 28 years.

*Parity and Gravidity.*—Four of our patients denied ever having been pregnant. On the other hand, there was a total of 103 gestations recorded. (We suspect that there were additional early pregnancies also which were terminated by induced abortion, but we could not obtain reliable figures to substantiate this supposition.) To the 34 married patients, 67 term babies were delivered. Generally speaking, the ability to conceive appears not to have been a problem either, although there was one case of primary habitual abortion in a para 0, gravida vi, from factors as yet undetermined. Another instance of secondary habitual abortion in a para iii, gravida viii, was seemingly caused by cervical incompetency.

*Symptomatology of Pelvic Pain.*—The duration of severe pain, judged at the time they were first seen, was one year or less in 8 patients. Seven others stated that they had had distress for over 3 but less than 5 years; 3 for 5 but less than 10 years; and 9 for over 10 years. The most persistent pain was described by a woman of 36, who complained of the selfsame ailment for 20 years. The median duration of pelvic pain in this series was 4.9 years.

Table II indicates that in 22 (61 per cent) of our 35 patients, the date of onset of the severe abdominal distress coincided with some crisis or definitely stressful event.



TABLE II. EVENT FROM WHICH MAJOR COMPLAINT DATED

<i>Operation.—</i>	
Salpingectomy ( ? postgonorrhea)	2
Hysterectomy, subtotal (menorrhagia)	2
Oophorectomy and ovarian resection (cysts)	1
<i>Pregnancy.—</i>	
Abortion ( ? induced)	2
Abortion (spontaneous)	1
Spontaneous delivery at term (illegitimate)	2
Spontaneous delivery at term (legitimate)	1
Premature delivery by cesarean section (antepartum hemorrhage)	1
Patient's acute illness or injury	4
Extramarital coitus (guilt)	2
Patient's first marriage	1
Patient's first divorce	1
Mother's commitment to mental hospital (psychosis)	1
Husband's injury and resultant chronic disability	1
No discernible event	13
Total patients studied	35

The discomfort described was usually aching to sharp and was generalized in the lower abdomen and pelvis. It was reportedly severe although rather vague in character, and usually recurrent or unabating in type. The major distress was not dysmenorrhea in its general description, although many times it was apparently aggravated by the menstrual periods after which it might continue for days.

Characteristically, the pelvic pain was only one of a multitude of symptoms which these 35 patients described. Myriads of secondary complaints involving every organ system were recorded. Table III lists these lesser ailments in order of their frequency.\* (Clearly, it would be impracticable to mention all the indispositions recalled during the present illness.)

No patient had only one or two complaints; many had half a dozen or more. It is difficult to rate such difficulties in order of severity, but the great variety is indicative of the complexity (as well as the simplicity) of the problem. Of course, the gynecologist is expected to concentrate on difficulties involving pelvic structures and the reproductive function. In keeping with this obligation, it is easy to imagine how tempted he might be to disregard many of the bewildering, seemingly unrelated, ancillary, more peripheral complaints. These, considered in their proper relationships, can be most meaningful, however.

The abdominopelvic pain was reported to be in the right lower quadrant in 20 patients, in the midline in 4, and in the left lower quadrant of the abdomen in 4 others. Bilateral distress was described by the remaining 7. The striking preponderance of pain in the right lower quadrant is obvious.

Typically, our patients were unable to delineate their discomfort. They tended to rub the lower abdomen or a part of the hypogastrium, indicating in a vague way the zone affected. Hence, point tenderness and regional landmarks were of little value to the diagnostician. Referral of pain was usually inconsistent, although occasional women did indicate its transmission to the back, bladder, rectum, or upper vagina. Understandably, the patients' poor description was exasperating to the physician.

*"Polysurgery" and Repeated Trauma.*—Only 2 women had never had an operation or serious injury. This is in keeping with the frequent observation that neurotic women with persistent or recurrent pelvic discomfort eventually

\*The similarity between this list and the one presented by Purtell, Robins, and Cohen<sup>9</sup> for their series of hysterical patients is all the more striking when we add that we became aware of the paper by these authors only after our data for the present group of 35 patients were under analysis.



come to operation, and operations are often multiple over the years.<sup>9</sup> "Polysurgery" (mostly pelvic operations) was sustained by 27 (82 per cent) of the 33 individuals who could not resist this experience. Such a sequence was found to represent 76 separate operations, or an average of 2.3 operations per patient. For each of these, a general or spinal anesthetic and an operating room had been required. This listing is presented in Table IV. (We have not included tonsillectomy or evacuation of retained products of conception from the uterus in this account. Hence, the data in Table IV are *underweighted* because only the single most important procedure was recorded in each case, even though two or more areas were involved. Thus, in one more particular—greater than average number of prior operations—did our sample of 35 patients resemble the hysteric ones studied by Cohen.<sup>3</sup>)

TABLE III. SECONDARY COMPLAINTS IN ORDER OF FREQUENCY REPORTED BY 35 WOMEN

Dysmenorrhea
Dyspareunia
Nervousness
Backache
Headache
Menometrorrhagia
Urinary frequency
Nausea and vomiting
Frigidity
Dizziness and fainting
Depression
Weakness, easy fatigue

TABLE IV. OPERATIONS SUSTAINED BY 33\* WOMEN

PROCEDURE	NO. OF PATIENTS
Dilation and curettage	18
Appendectomy	17
Hysterectomy, total	6
Cesarean section	5
Hysterectomy, subtotal	3
Laparotomy, exploratory	3
Hysteropexy	2
Breast biopsy	2
Culdotomy	2
Hemorrhoidectomy	2
Salpingo-oophorectomy, unilateral	2
Oophorectomy, unilateral	2
Herniorrhaphy	1
Salpingectomy, unilateral	1
Salpingectomy, bilateral	1
Tubal ligation	1
Resection of ovary, unilateral	1
Resection of ovary, bilateral	1
Splenectomy	1
Cauterization of cervix, extensive	1
Thyroidectomy	1
Sympathectomy	1
Laminectomy	1
Vein stripping	1
Total	76

\*Two of the 35 patients had had no operations. Of multiple procedures, only the most technical is recorded.

Three of our patients had had three or more curettages, and 6 had had three or more laparotomies. One had sustained five major surgical procedures. Yet, because of the extent of procedures, it is virtually impossible to tabulate accurately all the tissues removed. Nevertheless, we believe that it is important

to emphasize that almost all these operations were done because of the patients' complaints of pain and anxiety, or because of the doctors' lack of information, curiosity, or desperation. Would that we could estimate the beneficial results of this surgery! We can speculate upon the harm done.

*Further Gynecologic Considerations.*—We indicated earlier that no patient with palpable or definite medical or surgical findings seemingly capable of explaining the pelvic symptoms was included in this series. Free retroversion of the uterus, transient enlargements of the ovary, and a small cystocele or rectocele without uterine descensus were accepted. Even after completing the usual as well as certain other special procedures including operation, we were unwilling, *ipso facto*, to conclude that the patients' pelvic pain did not have a discernible somatic basis. For this reason, numerous qualified consultants (including a psychiatrist) also evaluated these patients. The positive psychiatric findings in each patient made by the psychiatrist were based on data which he elicited. Our medical colleagues also pronounced these women physically unremarkable. So, to the best of our knowledge, the 35 individuals displayed no abnormalities, or minor variations which seemed trivial with respect to their complaints.

Despite generally unremarkable physical findings, 7 patients did come to operation while under observation, however. Exploratory laparotomy was accomplished in 5 and culdotomy in 2 patients in an effort to establish the origin of the pelvic pain, either at our institution or elsewhere. This seems regrettable now, because nothing significant was found in any case.

In a minority of our patients, a diagnosis of the pelvic congestion syndrome was made. But, despite tenderness, a boggy uterus, leukorrhea, etc., in a few, the over-all picture was such as to indicate that these signs and symptoms were a part or a phase of the larger entity which we shall discuss further.

### Psychiatric Evaluation

A psychiatric interview was employed in the appraisal of each patient. The findings to be reported below represent a composite of the data obtained during the gynecologic work-up and subsequent psychiatric and psychological interviews.

*Behavioral Evaluation of the Patient.*—A most surprising and unexpected finding of our study was that the entire group of 35 patients seemed to have emotional or other life-stress problems, even as assessed in the first interview. After several interviews, it was possible to make a positive diagnosis of psychiatric disability in almost every case.

Unusual dramatic qualities were recorded in the appearance and clinical behavior of 18 (51 per cent) of the 35 women studied. Many of these "acted out" their problems, wore seductive garb, were remarkably slovenly, or were overly made up with cosmetics or hair bleaches. Most of these were curious or frankly peculiar in their appearance and demeanor. The majority of this group were agitated, anxious, apprehensive, overly talkative. Rarely could such people keep to the subject; they forever strayed to the description of yet another difficulty. Easy perspiration, hyperventilation, and blushing were commonplace during the interviews.

A minority of the patients were withdrawn, unduly quiet, and, in appearance, drab and downcast. A few described interpretations of their pelvic pain which were so illogical and unlikely as to suggest psychosis.

*Family and Social History.*—Evaluation of the family and other background material was essential to an adequate appreciation of the antecedents and the

setting in which the chronic pelvic pain later developed. In only 5 cases was the primary family group intact, reasonably secure, and happy. Large families (six or more siblings) were reported by only 5 patients. In average-sized families, one woman was the eldest and 3 were the youngest. They blamed this circumstance for at least a part of their problems. Divorce of the parents occurred in 5 families. This had direct bearing upon later happenings involving the patients' disorders.

In the etiology of this syndrome, none of the following factors in *themselves* appeared to be a consistent finding in most cases: the size and stability of the family; the ordinal position of the patient in the sibling sequence; and the lack of family financial resources. More important than these details themselves were the *attitudes* of each of the 35 individuals toward them.

The characterizations of important family members which follow represent (1) the image of these as given by the patient,\* and (2) our generalizations drawn from them.

*The mother:* The patient usually tried to identify with or emulate the mother or the mother substitute. She was unable to do this, however, because of constant wrangling, discord, and resentment between daughter and mother, and a struggle for recognition and independence by the girl. The mother, as described by many of the patients, was a critical, prudish, strict, short-tempered, unaffectionate, complaining, ignorant woman who showed little warmth or no real interest in her daughter's life and happiness. Thus, as seen through the eyes of the patient-daughter, the mother exerted a powerful and dominant influence on the patient during her childhood and adolescent years.

*The father:* This parent was frequently said to be humorless, ne'er-do-well, partially disabled, unemployed, and unsuccessful in a trade or small business. Many times a tippler or spree-drinker, he was disappointing in appearance and conduct. In the occasional contacts he did have with his daughter, he was thoughtless, punitive, and even brutal. He seemed to reject his daughter and thus had less direct influence on her than did her ever-present domineering mother. Open marital strife at home encouraged his drifting, drinking, and illicit associations with other women. In certain prominent instances, crime, death by violence, suicide, abandonment, or divorce eliminated the natural father from the scene. The stepfather did not seem to measure up to an adequate father-figure for the daughter.

A few exceptions to the above were described. These fathers were quiet, mild-mannered, colorless, overly serious or preoccupied men who were unexpressive and "too busy for children"—a daughter in particular. In one way or another, they evidently left most things at home to a controlling, dominant wife. Thus, in contrast to the mother who was a constant negative influence, the father was seen in both types of situations as a nonentity, for practical purposes.

Table V presents some of the patients' descriptions of their parents' notable characteristics.

*Summary of Childhood Experiences.*—The patients deplored their stormy, unhappy childhood, lack of affection, encouragement, and security at home. The mother or stepmother could usually be seen as the major stumbling block in the patient's emotional development. Guilt, however, now and again softened the patient's description of her mother. Obviously, most of these patients could not identify with their fathers either, and blamed them for the mothers' trials, unwanted pregnancies, and lack of financial and other support. A frequent statement by the patients was that they had had poor sex education. The suggestion that sex was "dirty" and the implication that this urge was a reason for the mother's and, indirectly, their own situation were also reported.

\*No adequate check on the validity of these characterizations is possible.



TABLE V. PATIENTS' CHARACTERIZATION OF THEIR PARENTS\*

	NO. OF PATIENTS	MOTHER	FATHER
Death of parent before patient's fourteenth year	5	1	4
Domineering, hypercritical	13	11	2
Cruel, punitive, miserly	5	1	4
Probable mental illness, alcoholism, epilepsy	13	5	8
Chronic invalidism	9	6	3
Religious fanaticism	5	4	1
Inadequate, nonentity	4	—	4

\*Table includes multiple descriptive statements of parents.

Repeatedly, as our results show, the daughter-patient "ran away" at an early age to get married. We would interpret this break for independence in many instances as flight from a lamentable home environment. The records indicate that this blind bolt for freedom usually led to a loveless marriage (or remarriage in the 12 cases of multiple marriage).

*The husband:* Time after time, the patient's husband was described by her as a kindly man—unlike her father—but not a virile, dominant male. He was a "nice guy," passive, quiet, easygoing, dependable, hard working, co-operative, friendly, and considerate. Nevertheless, he was periodically rebuffed by her. He demanded infrequent coitus and many times had premature ejaculation. This characterization of her husband as passive-accepting was in striking contrast to her image of a quarrelsome and rejecting father.

When describing their wives' complaints to the physician, the husbands seemed perplexed by the pelvic and other ailments. Yet, they were patient and unusually long suffering. Many were indulgent to an extreme. The husband sometimes even assumed care of the children during his wife's many illnesses. The marital relationship was less than good, but, except in a few cases, both parties seemed willing to put up with the union.

*Attitudes toward marriage:* The patient's unsettled family life in marriage was marred by her unsatisfactory sex attitudes, fear of harm by coitus, and aversion to pregnancy. These women were characteristically immature, dependent, and unable to cope with adult problems and responsibilities. This was particularly demonstrated in their attitude toward their children. The first one was not an undue burden, but numerous progeny were too much for this type of patient. Organization, adaptability, and perseverance were not attributes of these people. (Table VI shows that this latter is *not* due to inferior intelligence in these patients.) They remained uncertain, easily upset, unrealistic, confused, and dissatisfied with life and its obligations.

TABLE VI. OBJECTIVE PSYCHOLOGICAL TEST DATA

	FUNCTIONAL PELVIC PAIN (OUT- PATIENTS)	PSYCHIATRY (OUT- PATIENTS)	MEDICAL CONTROL (OUT- PATIENTS)	GYNECOLOGY (OUT- PATIENTS)
Patients	7	44	29	25
Mean age	33	40	42	25
Mean education	8	9	8	10
Mean I.Q.	94	97	97	98
Mean anxiety score	27	26	13	13
Mean No. psychosomatic symptoms	8	8	4	5
Mean Cornell medical index	72	51	34	32



**Diagnostic findings from psychiatric study:** Six had diagnoses of schizophrenia by the team-member psychiatrist who evaluated the 35 women in whom no medical diagnosis could be established. The remaining 29 were considered to be moderately or seriously disabled psychoneurotics. With few exceptions, these patients fell into the category of hysteria. One patient, however, was an obsessive-compulsive who shifted her difficulties to organic problems. A second patient had masculine strivings without being overtly homosexual. She experienced castration fears and fantasies with multiple operations.

### Psychologist's Evaluation of the Patient

After an experience involving 28 women, it seemed important for each patient also to consult a psychologist. This specialist, with standardized psychological assessment procedures, could obtain objective data to help in the identification, clarification, and amplification of the individual case review. The psychologist was given no prior information about each patient. Thus he obtained his findings without knowledge of the medical-psychiatric results.

The following battery of objective tests was used in the last 7 cases: (1) a short form (comprehension, vocabulary, and similarities) of the Wechsler-Bellevue Intelligence Scale<sup>14</sup>; (2) the Manifest Anxiety Scale<sup>15</sup>; (3) the Cornell Medical Index, Women's Form<sup>16</sup>; (4) the Saslow Psychosomatic Screening Inventory.<sup>17</sup> In addition, the psychologist employed (5) a structured interview with each patient, and (6) the Rorschach inkblot test.<sup>18</sup> The latter was used as an adjunct to the psychiatrist's interview and was included in an effort to identify cases of early psychosis.

Table VI summarizes the data derived from these tests applied to our last 7 patients plus three groups of controls. The control groups include a group of 25 randomly selected patients from the same gynecology clinic from which the 7 cases of pelvic pain were obtained; 44 randomly selected patients from a psychiatric clinic, and 29 randomly selected medical specialty (ophthalmology) clinic patients. None of the 7 patients with pelvic pain was psychotic. (For this reason, the Rorschach results are not included in Table VI.)

It is clear from Table VI that the objective psychological test findings corroborate the clinical psychiatric impression that patients with functional pelvic pain are psychiatrically disturbed individuals. Two of the control groups (psychiatric and medical control outpatients) with which the 7 cases of functional pelvic pain are compared in Table VI have been previously reported upon.<sup>19</sup>

It was shown in this earlier study that the Manifest Anxiety Scale,<sup>15</sup> a sensitive, highly reliable, 10 minute, 50 item personality inventory, significantly (.001 level of confidence) differentiated the psychiatric outpatient group (mean Anxiety score of 26) from the medical (ophthalmology) control group (mean Anxiety score of 13). This finding was cross-validated in a second study with two different psychiatric and medical groups.

Table VI indicates that the admittedly small preliminary sample of 7 patients with functional pelvic pain earned an anxiety score (mean of 27) as high as that of these known psychiatric patients. The gynecology control patients from the same clinic earned an anxiety score (mean of 13) which is half that of the pelvic pain group, and identical to that of the medical (ophthalmology) clinic control group (mean of 13).

The mean number of psychosomatic symptoms experienced by the pelvic pain group (8 symptoms) is again similar to the number reported by known psychiatric patients (8 symptoms), and is higher than the number reported by either the medical or gynecology control groups (4 and 5 symptoms, respectively).

The mean score of 72 symptoms checked by the pelvic pain group out of a possible 195 symptoms in the Cornell Medical Index questionnaire places this group well above the mean for the psychiatric outpatient sample. Scores as high as those earned by the 7 individual pelvic pain patients are so rare among groups of unselected medical patients as to be diagnostic of a psychiatric disorder by themselves. Even without statistical evaluation, the differences are clearly significant. This is because the mean of 72 symptoms reported by the pelvic pain group is derived from individual scores ranging from 49 symptoms for the patient with the lowest number to 117 symptoms for the patient reporting the highest number. So it is apparent that the pelvic pain patient reporting the fewest number of symptoms (49 symptoms) described more than the mean number of 2 (and almost 3) of the three control groups (means of 32, 34, and 51 symptoms).

In summary, the objective (preliminary) results presented in Table VI seem to constitute valid evidence that functional pelvic pain patients are individuals for whom a *positive* diagnosis of psychiatric disturbance can be made. That is, after due control for age (which has a zero correlation with the anxiety and psychosomatic measures used in this study), education, and intelligence, our pelvic pain group clearly resembles known psychiatric groups. The question might next be raised, "Now that it appears likely that brief personality screening inventories have a use in gynecologic practice in that they can alert the busy physician as to which patients to evaluate further for possible psychiatric concomitants, can they also tell him whether he is dealing with a psychotic or a psychoneurotic condition?" The answer is that they cannot.

The short, objective personality tests used in this study cannot differentiate one type of psychiatric disorder from another and thus in the individual case can serve only as a broad index of "likely presence or absence of a psychiatric disorder." A request, then, for a psychiatric consultation with the patients who earn scores close to, or above, the means for psychiatric patients shown in Table VI appears to be in order.

### Psychiatric Management

A rational program of psychotherapy must be based on an understanding and utilization of the dynamic factors with an approach which will break through the vicious pain cycle. The illustrative case indicates how the dynamic material was elicited with a simultaneous easing of tensions due to the emotional catharsis and freedom of expression afforded the patient. The attitude of the therapist was one of acceptance of the fact that the patient was really troubled and in pain; she was respected as a person, allowed to express hostility, and expected to begin standing up for herself. The patient recovered when she felt "whole" again—able to be herself and to be creative.

Our experience over 3 years' time has indicated that this pain problem is often difficult to handle and not easily referred for psychiatric assistance. The following features of management besides the psychotherapy of the patient are important:

1. The psychiatrist is a team-member of the gynecological clinic, and introduced to the patient by the referring physician. The patient does not have to go elsewhere for treatment and possibly get lost in the process.
2. Continued collaboration between the gynecologist and psychiatrist is important with repeat pelvic examinations by the former when warranted (if only to reassure the patient). The patient is requested to allow 3 to 4 months' study of her problem as a basis for an adequate evaluation, on a weekly or bi-weekly visit basis.

3. Contact with the husband or other important family member both to advise him (usually a worried and harassed man) of our impression of the patient's problem and to report progress in our joint program for therapy. Frequently, as in the case outlined, it proves helpful to have him participate for at least several visits with the social worker, both in terms of understanding his wife and his part in the conflictual situation (e.g., not talking when angry, like her mother).

*Illustrative Case.*—(No. 11—Scott, UC 245406.) A 25-year-old white housewife, para ii, gravida ii, was referred by her private physician with a history of progressively severe right lower quadrant pain for 18 months. This had been constant for 10 months, colicky, aching, worse in the late afternoon; aggravated by lifting or moving heavy objects, ovulation, fast walking, straining at stool, or by coitus. An appendectomy performed 7 months previously because of some nausea and vomiting associated with the pain revealed a normal appendix and mesenteric node. The patient felt well for 3 weeks after operation, only to have the identical pain recur. There was also a minor complaint for 6 years of alternating constipation and diarrhea, the loose stools lasting 2 to 3 days with evacuations up to four per day. Physical examination revealed some tenderness in the right lower quadrant and spasm of the right iliopsoas muscle. Laboratory studies were negative throughout, including complete blood counts, sedimentation rate, and urinalysis. X-rays of the lumbosacral spine, gall bladder, upper gastrointestinal tract and colon, and excretory urogram were all within normal limits. Orthopedic and surgical consultations disclosed no significant pathologic conditions.

Medical consultation brought out no significant new findings. The laboratory work, including a small bowel x-ray series, was again normal. Additional examinations by the orthopedist and peripheral vascular surgeon were normal. The patient gave a gynecologic history of menarche at 11, interval of 30 days, and a moderate menstrual flow of from 7 to 9 days with mild dysmenorrhea. The second baby had been born by a breech birth with some question of pressure on the right sciatic nerve. The gynecologic examination demonstrated a normal pelvis and genitals. The gynecology clinic referred the patient for evaluation to their staff psychiatrist.

The patient was seen a total of eight times in psychiatric interview, and her husband three times in collaborative therapy with the staff medical social worker. She had been married 8 years to a 34-year-old airline mechanic. Her 6-year-old daughter was asthmatic, and her 3-year-old son a very lively child. Her father, a 65-year-old chauffeur, was a passive person, dominated by the mother. She had always felt close to him, enjoyed activities with him, and in earlier years was regarded as a tomboy. Her mother was 54, a hypertensive, domineering critical person who had undergone a hysterectomy 5 years previously. Her only sibling, a sister aged 33, had been married for 12 years and had four children. The patient had been an average student in high school, and did clerical work for 3 years. Mental examination was normal, with an estimated average intelligence. There was, however, fear of snakes and dreams of killing animals or people with the car. The initial impression was "psychophysiological genitourinary reaction, chronic, moderate, manifested by right lower quadrant pain without organic findings, loss of sex desire, repressed hostility, tomboyishness, and dramatic qualities."

On the second visit, the patient pinpointed the onset of her pelvic pain as coinciding with emotional stress related to a very demanding older woman, an alcoholic neighbor, who imposed greatly on her, but whom the patient could not refuse out of fear. Her husband confirmed this story, and his own marked impatience with this situation. In subsequent visits, the patient revealed considerable anger at her mother for treating her father like a child, for being critical of the patient's handling of her children, and for smoking. In dream material and associations, she revealed concern about having small breasts, about having something taken away from her (by mother), and wanting something back she had given away.

On the sixth visit, the patient reported that she suspected she was pregnant—and 4 days later her pain left completely. The next visit, she reported a dream of being free from



her mother (who had opposed additional pregnancy until it became an actuality). She had been able in the interval to express anger openly to a "know-it-all" neighbor.

On the last visit, 4 months after beginning psychotherapy, she was still free of pain, and expressed more negative feeling about her mother (and in lesser degree, her husband) for quizzing her about her activities with an air of doubt, wanting to pick and choose her friends, and "sulking"—getting angry, remaining so, and keeping silent, sometimes for days.

The husband, in his collaborative interviews, confirmed much of the patient's story, adding that initially she was having difficulty in handling the children; was tired and doing a poor job of housekeeping so that he had to help excessively on weekends; and had avoided coitus for the previous 6 months. Under therapy, she had become less nervous and depressed. Because of his work interfering with clinic visits, he withdrew after his third session, when he reported that coitus had been resumed satisfactorily, that he and his wife were communicating with more ease, and that their total adjustment was much improved.

### Therapy

Admission of one of the 6 psychotics to a mental hospital was necessary to obtain special intensive psychotherapy. Three other schizophrenic patients were treated by psychiatrists on an ambulatory basis. The other 2 denied the need for treatment.

Short-term psychotherapy for one-half to one hour weekly was arranged for 12 of the 29 psychoneurotic patients who were willing to accept this program. These meetings were scheduled when minor gynecologic conditions were being investigated or treated, or during regular return visits.

The other 17 patients rejected psychotherapy, were "insulted" at the implication that their illnesses might have emotional or life-stress concomitants. Most of these women continued their "medical shopping," consulting doctor and quack, seeking further surgery or medical treatments for their supposed ovarian, uterine, or other pelvic disorders.

### Results of Treatment

The one psychotic patient who did enter a mental hospital was unimproved after one year. Three others were somewhat better after psychotherapy in the outpatient clinic. One psychotic woman improved without any treatment, presumably because of a more favorable home situation.

Twelve of the 29 psychoneurotic individuals were booked for outpatient psychotherapy; 11 were seen two or more times by the psychiatrist, and 6 were definitely improved by clinical judgment. Three were well, to all intents and purposes. One of these, however—a woman who had had only five treatment sessions—was promptly "cured" when she achieved a much-wanted pregnancy. So, in this instance, the case may or may not have been an example of successful psychotherapy.

Four of the remaining 17 psychoneurotic patients improved without psychotherapy—one also upon becoming pregnant—and 3 were better after supportive help by the gynecologist alone. These 4 "spontaneous" cures out of 17 is the usual proportion expected in "untreated" neurotic individuals.<sup>20</sup>

### Comment

*Psychodynamic Factors.*—While it is readily apparent in the majority of our cases that the pelvic pain is experienced in a chronic life-stress situation related to conflict with a mother-person, the exact basis for the choice of symptom and site from a dynamic point of view is uncertain, because our study is cross-sectional rather than analytic and longitudinal. Frequently, though, the patient has been able to point out, in addition, an acutely stressful problem



corresponding in time to the onset of her pain. It seems probable from our material that the location of the pain is connected with conflicts over femininity and independence. The mothers of our patients are described as strict, critical, and controlling, and with attitudes that sex is something nasty, unpleasant, and to be avoided. It is not surprising, therefore, that their daughters are rebellious, guilty over their rebellion, and guilty about their sexual impulses (and have symptoms of pelvic pain, dysmenorrhea, dyspareunia, etc.). It is as though the daughters are in conflict about their wholeness (castration anxiety), including their right to control and enjoy their own bodies, to have their own opinions, and to own their own souls. If there is any specific bodily "site" in actuality or in mental imagery for femininity, this must certainly be primarily in the pelvis. It is well known that conflict produces tension which in turn can produce real pain—whether the actual spasm is in the bowel, the uterus, the iliopsoas muscle, or elsewhere (and a conditioning factor may well be responsible for the actual tissue involved in spasm).

It seems that a vicious cycle is instituted in which the natural impulses toward freedom of self and sexuality can be realized only by fighting a domineering mother-person whom the daughter is supposed only to love—with the result that if she surrenders in her struggle for maturity, she is frustrated and angry, and internalizes her rage; and if she persists in the battle, she is made guilty by the mother (now incorporated as part of her conscience) for having angry thoughts and wanting to enjoy her sexuality. Being impaled on either horn of this dilemma can certainly produce conflict, tension, and pain.

*Psychological Conditioning.*—To the adult woman with hysteria, pelvic (and other types of functional) pain is actually perceived and experienced in a subtle way which, however, often defies the efforts of her physician to discover the mechanism. It has now become clear that pain can occur in a context of purely psychological experiences.<sup>21, 22</sup> Thus, such stimuli or cues as "a person," "an actual argument," even "a thought" about some affectively toned experience have been shown in the laboratory to produce physiologic changes in a variety of body systems.

While the theoretical bases for these phenomena are not yet clearly defined, it seems likely that a model much like Pavlov's classical conditioning experiment may provide the soundest basis of understanding. Just as he was able to elicit the physiologic response of salivation from his dogs in relation to a previously neutral cue (the sight of his trainer) by pairing it (trainer) with another appropriate stimulus (food), so a series of similar early conditioning experiences may have occurred in our patients. Some previously neutral cue could have occurred (a thought, a member of the family, etc.), which was paired in time with a bodily stimulation sufficient to elicit the pain responses, and may develop the power to evoke the physiologic changes which she then perceives as pelvic pain. Patients need not be aware of the cues which elicit the pelvic pain. This is concluded from the many recent studies on "conditioning of physiologic responses without awareness," a phenomenon which psychologists now call "subception" or "subliminal perception."<sup>23</sup>

To suggest that the pelvic pain experienced by most of our patients occurs as the end result of a complex organism-environment relationship in which conditioning or other forms of learning play a prominent role, does not imply that the pelvic pain is "unreal" or "imaginary." The bodily changes and accompanying sensations are genuine indeed and many of these can be produced in the laboratory.

Furthermore, Cohen and his associates<sup>2</sup> have indicated that the practical clinical description of hysteria does not imply "hysterics." In accordance with

modern concepts, hysteria includes definitely recognizable clinical characteristics, signs, and symptoms. The symptom complex shown by a woman on whom a positive diagnosis of hysteria is made<sup>9</sup> is almost exactly that exhibited by the majority of our patients and reported in Table II.

These women, as Chodoff and Lyons<sup>24</sup> have stated, are "usually vain, egocentric, display labile and excitable yet shallow affectivity, whose dramatic attention-seeking and histrionic behavior may go the extreme of lying and even fantasy. They are very conscious of sex, and are essentially provocative yet unresponsive sexually and are dependently demanding in their interpersonal relationships." We have also found this clinical behavior picture to be typical of the patients in this study.

Because of the common association of rather similar secondary complaints reported by individuals with anxiety neurosis<sup>25</sup> and hysteria,<sup>2</sup> we should clarify these two syndromes. Anxiety neurosis (anxiety tension state) does occur in men. (In our experience, one out of 3 patients with anxiety neurosis coming to a physician is male.) It is more common in women, however. Patients with anxiety neurosis, whether men or women, generally report difficulties involving the upper part of the body: the head, chest (breathlessness and tachycardia), and epigastrium. *These symptoms are always given clearly and definitely.* In almost every case, a feeling of "nervousness," panic, or dread is precisely described—although with a statement, "I can't understand why I feel this way."

In contrast, hysteria is found most often (some writers believe only) in women. Female patients with hysteria concentrate their main problems within the abdomen and pelvis. Actually, *they describe these symptoms imprecisely* with colorful dramatic embellishments. When asked to be more specific, they simply shift the topic to unrelated details of the past. Headache, dysphagia, palpitation, epigastric discomfort and urinary frequency, and symptoms of autonomic overactivity are described by both types.

We must repeat that the female hysteric patient is *experiencing* her symptoms, although the physiologic mechanism for this psychophysiologic experience (pain) is still unknown. There also is no denying the tenderness and turgescence of the genital structures in many cases of obscure pelvic pain.

Although we agree that there is a vasodilatation and sensitivity of the pelvic organs in certain patients with chronic functional pelvic pain, we are not convinced that this is commonplace. Many women report only right- or left-sided pelvic pain, for which no physiologic mechanism can be established. Regional congestion on one side of the pelvis has rarely been seen in such cases at laparotomy. Even after repeated examinations, we were not persuaded that the majority of our cases in this series were examples of the syndrome of pelvic congestion.

Nevertheless, the appearance of the tissues may be helpful in identifying certain of these women with emotionally induced discomfort. But this observation alone will not be enough. It will not emphasize the previous conditioning of the patient, or the setting in which the difficulty began.

### Conclusions

The woman with pelvic complaints out of proportion to her physical findings is emotionally ill. Taylor and others<sup>3</sup> admit this to a degree, but they seem unwilling to accept a psychiatric modality for the illness. We believe that most of these women are hysteric, and that a Pavlovian conditioning experience, imposed upon an individual with a personal-social background of the type earlier described for our 35 patients, may well be the means whereby the pelvic pain persists in the "absence" of apparently relevant physical findings.

We cannot escape the conclusion that many pelvic pain problems, as well as pelvic congestion cases, are "bodily reactions to stressful life situations,"<sup>73</sup> because of the make-up and conditioning of these patients and their reactions to pressures in living. Some variations are to be expected, but all of our patients displayed emotional immaturity, dependency, and inadequacy as wives and mothers. It is likely, however, that women who are wanting in a sexual or reproductive sense should concentrate their concern and attention within the pelvis. As a result, further genital complications may result.

Functional pelvic pain of the type described has been considered to be "organ language" with a final outburst inspired by a specific unpleasant situation. Emotional difficulties then precede the actual onset of the discomfort. In the light of such observations and deductions, we believe that the psychological factors are the etiological precursors, rather than the results, of somatic disease.

Although it is possible to arrive at a diagnosis by the progressive elimination of the more likely physical disorders (a very dangerous procedure in many cases), a *direct* diagnosis of psychoneurosis based on positive psychiatric criteria is more logical and far easier in cases of suspected functional pelvic pain. This, together with a proper evaluation of the physical findings, should lead to a better appraisal and treatment of the patient. Where a positive psychiatric diagnosis cannot be made in a woman with "functional" pelvic pain, "organic" mechanisms other than psychological should be sought.

### Summary

1. Thirty-five women with chronic functional pelvic pain were studied by medical-psychiatric-psychological procedures in a gynecologic outpatient clinic over a 3-year period.

2. All of these patients were found to have disabling psychiatric problems.

3. Twenty-nine were diagnosed as psychoneurotic (almost all being hysterical), and 6 were found to be psychotic (schizophrenic).

4. Patients with functional pelvic pain almost invariably resist the conclusion that their discomfort occurs in a psychophysiologic (life-stress) context.

5. Once the diagnosis of an emotional disorder (rather than gynecologic disease alone) has been firmly established, appropriate treatment will be greatly enhanced.

6. Approximately half of our patients with chronic functional pelvic pain were amenable to short-term psychotherapy and half of these were definitely benefited by such treatment.

7. It is postulated that the "mechanism" for functional pelvic pain may very well be the classical Pavlovian conditioning model, whereby a psychophysiologic response (pelvic pain) is elicited by previously neutral cues (people, a thought, etc.). The laboratory work ("subception" and "conditioning without awareness") on which this hypothesis is based is still in the preliminary stages.



8. A basic interest and understanding of the psychiatric aspects of gynecology is vital for the proper diagnosis, prognosis, and treatment of the women with chronic functional pelvic pain.

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### Discussion

DR. FRANK R. LOCK, Winston-Salem, N. C.—Dr. Benson and his associates have made a thorough gynecologic and psychiatric study of 35 women with chronic disabling pelvic pain. In none of these women was there clinical evidence of organic disease. The psychiatric evaluation proved that the entire group of 35 patients “seemed to have emotional or other life-stress problems.” This was evident in the first interview, and confirmed by subsequent evaluations by the psychiatrist and psychologist. Although these patients were selected as definite and striking examples of this problem, Dr. Benson’s study confirms the conviction of many of us that adult women with hysteria and other types of functional disease actually perceive and experience pelvic pain “in a subtle way which defies the efforts of her physician to discover the mechanism.”

He considers a number of possibilities “whereby a psychophysiologic response (pelvic pain) is elicited by previously neutral cues.” This is of more than academic interest since operative treatment has been recommended at times when circulatory phenomena represent the only objective finding, and with slight consideration of psychiatric features of the cause-effect relationship.

We appear to be on the threshold of a better understanding of a situation which seems to me to be quite comparable to the problem of headache in the field of general medicine. That “tension headache” and migraine appear in functional disease is accepted. As a result, the mystery and confusion concerning these conditions has largely disappeared; an intelligent and fundamental approach to the problem has evolved. Discrete psychophysiologic changes have been observed in each type, which explain the mechanism for the headache. The aura which precedes migraine is related to vascular spasm in the occipital area of the brain. Dilatation and increased pulsatile flow in the temporal artery, or other branches of



the external carotid, are associated with the pain. Objectively proved spasm of the lumbo-dorsal muscles in the neck precedes and continues in the course of tension headaches. The probability that similar painful peripheral changes in the pelvic viscera result from emotional stimuli is suggested by the changes in thermal conduction of the vaginal wall reported by Duncan and Taylor.

In view of the suspicion that the pelvic viscera are etiological factors in personality disorders, which has existed for many centuries, it is remarkable that studies of the type presented by Dr. Benson are necessary. He has shown us, however, that there is no simple method available to us for detection of the patient whose pain is the result of functional disease. He has shown once more that these patients are given the benefit of "polysurgery" with an average of 2.3 operations per patient without relief of their symptoms. Exploratory laparotomy was performed in 5, and culdotomy in 2 of the patients while they were under observation in his institution or elsewhere. Their observation confirms our limited experience, in which nothing of significance is found by exploration in absence of clinical findings in any patient.

I will look forward to the report on the statistical importance of functional disease in their clinical experience, which he suggests may be forthcoming.

Obstetrician-gynecologists are generally aware of the psychic component in all organic disease processes. Dr. Benson's study will further document the importance of functional disease in gynecologic practice.

DR. FRANK R. SMITH, New York, N. Y.—This discussant believes with many others that all pelvic pain evolves from some form of pelvic congestion, localized or general, and manifests its localization by the so-called visceromotor reflexes, and that these impulses are initiated by disturbances of vascular physiology.

While the possibility of multiplicity of contributing factors cannot be overlooked, one source usually predominates. It is my feeling that the psychiatric factor is frequently a contributing or aggravating factor but rarely, if ever, a primary factor.

Cohen and his co-workers seem practically alone in their belief that pelvic discomfort may be a manifestation entirely psychogenic in origin and hysterical in character without somatic components, and that the pain is imaginary and exists only in the patient's mind. The essayist has mentioned the experiments in which Duncan and Taylor, using a method dependent on changes in thermal conductance, showed that variations took place whenever, during a psychiatric interview, subjects were touched upon toward which the patient had special emotional attitudes. These pelvic vascular experiments during psychiatric interviews tend to point to pelvic vascular physiology as the etiological factor in pelvic pain, and to refute the belief of Cohen and his associates that pelvic pain is purely imaginary in some patients. These same experiments, however, help to prove that emotional disturbances may, in certain cases, be the origin that triggers the mechanism of pelvic pain like other extra-genital factors and should be so classified. In the opinion of the speaker perhaps the psychiatrist should not be the last to be consulted but he certainly should not be the first.

The management of pelvic pain should consist of simplicity of therapy before resorting to surgical, hormonal, or psychiatric methods, and, if a multiplicity of causes is recognized, appropriate therapy for each etiological component should be employed.

DR. BENSON (Closing).—It might be of interest to mention that some differentiation must be made between the patient with anxiety neurosis and the one with hysteria. A vascular phenomenon in both cases can (but need not necessarily) be noted.

I should like to clarify certain points which I may not have adequately stressed:

A. Free retroversion or transient enlargement of the ovaries, in our opinion, could not by any stretch of the imagination have caused the degree of pain, the localization, or the many secondary difficulties reported. Almost all of these patients had been operated upon repeatedly and nothing was found. Hence, we believe that inconsequential anatomic variations do not constitute erroneous case inclusions.

B. When pelvic congestion is observed in emotional patients, such as Dr. Taylor and we have described, this will be of considerable help in diagnosis. Nevertheless, not all women with functional pelvic pain will exhibit vaginal or pelvic congestion. Many women report only right- or left-sided pelvic pain. Regional congestion on one side of the pelvis only has rarely been seen to explain the problem.

Difficulties in the patient's background and the setting in which the illness began may or may not be dramatic. It is the patient's reaction to this environment and stress which is important. This, we must seek out. We believe hysteric patients internalize their difficulties. How this is accomplished can be debated. The point is that they do this and have "real" pain.

I, too, would hate to see the psychiatrist the first or the last physician to care for the gynecologic patient. I am still a gynecologist-obstetrician who intends to care for patients himself. I do believe, however, that certain psychiatric investigational methods, explanations, and modes of treatment are of value and that we should use them too. Indiscriminate symptomatic medical treatment and surgery of the "let's do it because someone else will do it" type should be avoided in the management of the patient with pelvic pain for which no somatic mechanism can be found.

## MEDULLARY RESECTION OF THE OVARIES IN THE STEIN-LEVENTHAL SYNDROME\*

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IN 1935 Stein and Leventhal<sup>1</sup> first presented their observations on the syndrome which has since borne their name. The syndrome is characterized by infrequent periods or amenorrhea, moderate to severe virilism, occasionally menometrorrhagia, some obesity and sterility, and enlarged polycystic ovaries. Because of the lack of any fully recognizable endocrinopathy, and because of the enlargement of the ovaries, they introduced the operation known as wedge resection. Surprisingly enough the operation, which removed much of the ovarian tissue of patients who already had ovarian deficiency, resulted in a prompt appearance of normal menstrual cycles in a majority of the patients. Numerous subsequent reports<sup>2-9</sup> detailing the results of wedge resection of the ovaries in patients with the syndrome have, in general, confirmed the existence of the syndrome and the beneficial results of wedge resection. When we recall that the original paper appeared before very much was known about the androgens, and even less about the corticoids, their accurate description of the syndrome and their successful treatment of it seem all the more remarkable.

The etiology of the syndrome is obscure. The thickened, smooth capsule of the ovaries has led some authors to believe that the failure of ovulation and resultant sterility are due to difficulty in extrusion of the ovum. Du Toit,<sup>10</sup> in particular, has put forth the idea that the thecal cone of Strassmann is abnormally oriented and that the thickened tunica is secondary to multiple follicular cysts. Others<sup>5</sup> have presumed that there is some abnormality of the circulatory apparatus which produces the cystic follicles. Still other authors<sup>8, 11</sup> have suggested that the changes in the ovaries are secondary to pituitary dysfunction. None of these theories, however, helps very much in explaining the successful results from wedge resection beyond the possibility that wedge resection does remove much of the thickened capsule of the ovaries.

### A New Theory of Etiology

Our own ideas gradually developed as we came to realize that the disorder in this syndrome is definitely separate from the ovarian dysfunction associated with simple obesity, hypothyroidism, or the temporary disturbances

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which occur during adolescence or the climacteric. The fact, too, that in the first cases which we recognized there was considerable virilization naturally led us to see a similarity between them and other cases in which testosterone was being administered for one reason or another. This led us to theorize that perhaps the ovaries of these women with the syndrome produced a little too much androgen. This theory is not especially visionary because the production of too much androgen, as from an arrhenoblastoma or a virilizing adrenal tumor, induces rather abrupt amenorrhea and virilism. If one assumes, therefore, that the ovary produces just enough extra androgen partially to inhibit the pituitary, one could expect ovarian dysfunction and symptoms of the type found in patients with the syndrome.

This theory gathered some support when we came to operate on a few patients. The ovaries, to us, looked much like oversized testicles. The tunica albuginea was smooth and gray and numerous small vessels were seen coursing through it in much the same way as the vessels course through the tunica of the testis. Then, when an incision was made through the cortex of the ovary, we found that the medullary portion was larger than in the normal ovary. The removal of this oversized medulla, without resection of the cortex, resulted in prompt appearance of normal menstrual cycles. These good results in a few cases from medullectomy, which, in fact, should remove that portion of the ovary most likely to contain tissue remnants of the embryonic testis, made us think that the ovaries of patients with the syndrome might be a special variety of ovotestis. This is a logical speculation. The medullary portion of the ovary is the remnant of the testicular portion of the indifferent gonad. In the male this primitive tissue becomes the testis, whereas in the female this tissue develops initially in the same way as in the male, but then becomes atrophic as the ovarian cortex develops around it. Our theory says only that for some reason, probably genetic in origin, patients with the Stein-Leventhal syndrome have tissues in the medulla of the ovary which produce too much androgen. If that androgen happened to be testosterone, only a small amount would be required to disrupt the menstrual pattern and produce the mild virilism which many of these patients exhibit. Removal of the medulla, therefore, should reduce the production of excess androgen, and thereby permit normal functioning of the ovarian cortex.

### Material

The patients whom we have subjected to the operation of medullary resection certainly belong to the group described by Stein and his associates (Table I). Puberty began at the usual time. The pubic and axillary hair appeared at the normal time. The breasts developed normally and the first menstrual period occurred between the ages of 11 and 16 years. Patients who had an excess of hair on the body stated that this hair became apparent by the age of 14, but more pronounced with added time. The clitoris was appreciably enlarged in 13 cases and noticeable hirsutism was present in 20 cases. Also the laboratory studies revealed a normal basal metabolic rate and normal 17-ketosteroids in all the cases studied. The menstrual periods were fairly regular in a few cases. It is of interest, also, that many of the patients had had



dysfunctional bleeding for many years. One is certainly impressed with the fact that the menstrual pattern was very abnormal in nearly all of the cases from the very beginning. The ovaries were enlarged in 16 of the 22 cases.

The operation thus far has been carried out on 22 patients. Only those considered to have grossly typical ovaries are included in the study. There are a few other patients who were thought to have the syndrome, but who at operation were found to have normal-appearing ovaries, except for the lack of ovulation.

TABLE I. HISTORY AND PREOPERATIVE FINDINGS

CASE NO.	AGE AT MENARCHE	CYCLE AT AGE 14-18	PROLONGED BLEEDING BEFORE OPERATION	VIRILISM*		ENLARGEMENT OF OVARY	AGE AT OPERATION
				CLITORIS	HIRSUTISM		
1	13	1-5 months	+	0	2+	3+	29
2	15	3-4 months	0	3+	4+	2+	29
3	12	4-7 weeks	0	3+	2+	0	29
4	14	1-6 months	0	1+	2+	1+	32
5†	14	Regular to age 17	0	2+	3+	3+	34
6†	11	14 days to 6 months	+	1+	3+	1+	24
7	13	1-4 months	+	0	3+	1+	33
8	13	1-3 months	0	3+	1+	0	35
9	11	Regular to age 18	+	3+	2+	0	25
10	13	3-4 months	0	1+	2+	1+	26
11	13	Infrequent	+	0	1+	0	29
12	12	Infrequent	0	0	1+	1+	26
13	15	Infrequent	0	1+	3+	1+	20
14	11	Regular to age 24	+	0	3+	1+	26
15	13	Irregular	0	0	2+	1+	30
16	13	2-9 months	+	0	2+	1+	33
17	16	1-3 months	0	2+	2+	2+	27
18	14	1-3 months	+	0	1+	1+	28
19	11	1-4 months	+	3+	2+	0	31
20	12	5-6 months	+	1+	0	1+	24
21	13	2 months	+	1+	0	1+	25
22	14	3-5 months	0	0	1+	0	26

\*17-Ketosteroids normal in 20 cases, not determined in 2 cases.

†Hypertension both before and after operation. Also appearance similar to that of Cushing's syndrome.

### Method

The operation is carried out in the following manner. A longitudinal incision is made through the capsule and carried down through the cortex. When the medullary portion is reached, usually about 8 to 10 mm. beneath the surface of the ovary, the medullary connective tissue is resected by sharp dissection. The medullary tissue is excised as completely as possible. In some cases several grams of medulla could be removed from each ovary without sacrifice of any of the cortex. Bleeding points are controlled with fine sutures and the bisected ovary restored with a few mattress sutures. Usually the ovary is normal in size after removal of the core of medullary tissue.

### Results

There have been few immediate or late complications attributable to the operation. Only one patient has developed a cystic ovary. This ovary was removed elsewhere 3 years after the medullary resection. The cyst proved on microscopic examination to be a cystic corpus luteum. Another patient had intestinal obstruction a year following operation and required a laparotomy.

The results following this operation have to be judged primarily by clinical evidences of restoration of normal periods. These are given in Table II and Table III. The number of spontaneous periods in the year preceding operation are correlated with the number of periods in the first year, second year, etc., following operation. In all cases a normal menstrual period occurred between 15 and 45 days after the operation. In only 2 cases did bleeding occur within a few days after operation. The frequency of the periods following operation is indicated by the number occurring each year. In nearly every case the cycle appears to be fairly normal and certainly much more normal than before operation. Likewise, it was unnecessary to give progesterone, or estrogen and progesterone, to control dysfunctional bleeding or to induce periods except on rare occasions. In contrast, before operation, these hormones were used repeatedly.

TABLE II. CASES FOLLOWED FOR 3 TO 6 YEARS

CASE NO.	YEAR OF OPERATION	CYCLES IN LAST YEAR BEFORE OPERATION	NO. OF CYCLES YEARLY FOLLOWING OPERATION					
			1	2	3	4	5	6
1	1952	0	11	10	Ab.	?	?	?
2	1952	0	14	13	14	13	12	13
3	1952	4 S*	13	Preg.	12	12	Preg.	12
4	1953	3	13	9	8	9	12	—
5	1953	2	13	12	13	Preg.	13	—
6	1953	24	11	8	13	7†	5†	—
7	1954	5 S	12	10	9	9	—	—
8	1954	7	12	10	11	11	—	—
9	1954	5 S	14	14	13	13	—	—
10‡	1954	2	12	11	10	10	—	—
11	1955	18	9	7 Preg.	3	—	—	—

\*S, Spotting.

†Occasional episodes of prolonged bleeding.

‡Wedge resection in 1952 with temporary improvement.

TABLE III. CASES FOLLOWED FOR LESS THAN 3 YEARS

CASE NO.	YEAR OF OPERATION	CYCLES IN LAST YEAR BEFORE OPERATION	NO. OF CYCLES YEARLY FOLLOWING OPERATION	
			1	2
12	1956	3	12	8
13	1956	2	13	13
14	1957	PS*	12	—
15	1957	6	13	—
16	1957	PS	6	—
17	1957	4	12	—
18	1957	2	1	Abortion at 3 months now 7 months pregnant
19	1957	4 S†	13	—
20	1957	3 S	11	—
21	1958	0	13	—
22	1958	0	Recent case	

\*PS, Episodes of prolonged spotting or bleeding.

†S, Spotting.

The results obtained following operation have been the same regardless of the type of menstrual disorder present before operation (Table IV). There were 13 patients with very infrequent periods in the year prior to operation. The average was 12.6 cycles in the year following operation. There were 7 patients with occasional episodes of spotting. These averaged 11.6 cycles in the year following operation. There were only 2 cases in which virtually all cycles were short. These 2 averaged 10.2 cycles during the first year after operation.

TABLE IV. MENSTRUAL CYCLES PRE- AND POST-OPERATIVELY

CASE NO.	CYCLES IN LAST YEAR BEFORE OPERATION (AVERAGE NO.)	CYCLES IN FIRST YEAR AFTER OPERATION (AVERAGE NO.)
<i>Patients With Infrequent Periods.—</i>		
1, 2, 4, 5, 8, 10, 12, 13, 15, 17, 18, 21, 22	2.4 (13)*	12.6 (11)†
<i>Patients With Only Episodes of Spotting.—</i>		
3, 7, 9, 14, 16, 19, 20	3.3 (7)	11.6 (7)
<i>Patients With Short Cycles.—</i>		
6, 11	21 (2)	10.2 (2)

\*Numbers in parentheses are numbers of cases.

†Two cases excluded; one patient had an abortion at 3 months followed by a normal pregnancy. The other is recent.

Little real regression of virilism was shown. Those who had rather marked virilism had regression in the size of the clitoris, but little change in facial and body hair. Some patients have stated that the facial hair seemed to grow less and seemed to be finer and softer. One patient in particular (Case 3), did lose much of the hair on the sides of her face and after 5 years shows virtually no evidence of facial hair other than a few sparse hairs on the chin and upper lip which she removes with tweezers.

The results in the correction of infertility have been moderately good. Of the 22 patients there are 12 who are married and who wished to have children. Of these, 3 have been delivered of four normal children, and another is now in the seventh month of pregnancy. There were two early abortions and one premature stillbirth at 5½ months. The others either were single or did not wish to have children. The salvage rate is not as good as one would hope for, but it is fairly good. Quite possibly, of course, some of those who have so far failed to conceive may do so, because several are presumed to have ovulatory cycles as determined by basal body temperature.

The histological appearance of the resected medulla in these cases possessed one common feature. In each instance there was hyperplasia of the stromal cells to a greater or lesser degree. Luteinization of the medullary stromal cells was generally apparent. Occasionally hyperplastic luteinized perifollicular thecal-cell collars were noted. Unequivocal Leydig-cell nests were identified in several cases in addition to one case with a Leydig-cell adenoma. Stains for fat were made in many of the cases. These showed numerous focal areas of sudanophilic material in tissue which appeared to be stromal connective tissue by hematoxylin and eosin stains. The ovarian microscopic findings are in accord with those described in the literature pertaining to the Stein-Leventhal or to the hyperthecosis<sup>12</sup> syndrome, including the occasional finding of a corpus luteum.

The case with a Leydig-cell adenoma (No. 3) is especially interesting. This patient had a cycle of 28 to 40 days without abnormal bleeding from puberty to marriage. Soon after marriage, she conceived and was delivered of a normal child. Following lactation there were a few normal menses. Then the periods ceased except for occasional episodes of spotting. At the same time considerable virilism appeared. After about 4 years a laparotomy was performed. A small Leydig-cell adenoma about 10 mm. in diameter was found in the medullary portion of the right ovary. This could not be readily detected by inspection or palpation of the ovaries, and would probably not have been discovered except by medullary or wedge resection of the ovary. Following excision of the ade-

noma the menstrual cycles reappeared and became regular with an interval of 28 to 30 days. Since operation the patient has had two more normal children. There has been no evidence of any recurrence of the tumor in 5 years.

### Comment

The interval between operation and the appearance of the first menstrual period does give some indication of the type of endocrinopathy present in the ovary. If the operation removed a source of progesterone one would expect withdrawal bleeding to occur in 2 to 4 days. In only one case did withdrawal bleeding occur this soon and in that case an active corpus luteum was removed. If the operation removed a source of estrogen, bleeding should occur, provided the estrogen level were adequate, in about 7 to 8 days. Bleeding did

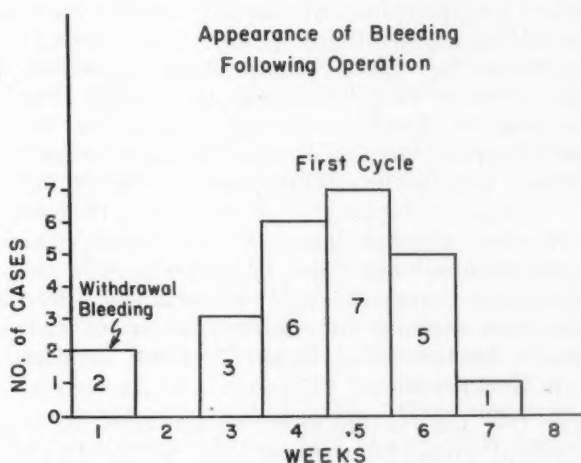


Fig. 1.

occur in one case 8 days after operation. In the remaining 20 cases, bleeding occurred between 15 and 45 days after the operation (average 30.1 days) (Fig. 1). This, of course, strongly suggests that the operation did decrease the level of some steroid which was exerting an inhibitory effect on the functioning of the ovarian cortex. The fact that removal of this steroid was not followed by withdrawal bleeding suggests that this steroid has the capacity to suppress ovulation with a dosage that does not give withdrawal bleeding.

The chemical nature of the supposed steroid is obscure but certainly an androgen would be under suspicion. It is well known that proper doses of testosterone or methyltestosterone will disrupt the menstrual cycle and produce virilism without being followed by bleeding on withdrawal of the hormone. Also, in the postmenopausal women primed with estrogen, testosterone propionate does not induce withdrawal bleeding unless 50 to 100 mg. is given in a single dose.<sup>13</sup> It is quite reasonable to suppose, therefore, that an androgenic component is removed from the ovary by resection. The best evidence, however, that the removal of the medulla does eliminate, or remarkably reduce, the production of an androgen with gonadotrophin-inhibitory powers is obtained by comparison of the time interval between cessation of treatment with estrogen or androgen in normally cyclic women and the appearance of the first period. We have a small series of patients with endometriosis who were treated with large doses of stilbestrol to suppress ovulation. These patients had their first spontaneous period between 24 and 49 days after cessation of therapy.<sup>14</sup> This



interval is virtually the same as in these cases operated upon, i.e., 15 to 45 days. We also have in our own series of virilizing tumors, 3 cases of arrhenoblastoma, 2 cases of adrenal tumor, and one case of an adrenal rest tumor of the ovary, all in the reproductive years. None of these patients had withdrawal bleeding in the immediate postoperative period but all of them had their first period between 18 and 61 days following removal of the tumor. We must conclude then, until better evidence is forthcoming, that the beneficial effects of medullectomy are achieved by elimination of, or by reduction of the amount of, a gonadotrophin-inhibiting steroid that clinically simulates a potent androgen.

Undoubtedly there are many cases simulating the Stein-Leventhal syndrome in which resection of the ovaries has no beneficial effect. In fully developed cases of Cushing's syndrome, adrenalectomy with substitution therapy results in virtually complete regression of the virilism, obesity, and hypertension, and in the prompt reappearance of normal ovarian function. Similarly, in cases of female pseudohermaphroditism (congenital adrenal hyperplasia) the administration of cortisone or related compounds suppresses the output of ACTH, decreases the urinary 17-ketosteroids to normal levels, and ovarian function returns to normal.<sup>15</sup> These examples indicate that in these cases correction of the adrenal hyperfunction results in normal ovarian function. There are other cases of virilism with menstrual dysfunction which simulate the Stein-Leventhal syndrome. There are reports<sup>7, 16-19</sup> indicating that suppression of the adrenal is beneficial in some of these cases. Unfortunately, this procedure was carried out in only one of our cases (No. 18), and in this case the menstrual dysfunction was unchanged. Apparently, therefore, the procedure of adrenal suppression offers the best method for differentiation of the cases in which ovarian resection would be beneficial from the cases in which little benefit might be expected from the operation.

A good laboratory test for the diagnosis of the cases in which ovarian resection should be beneficial would be of great help to the clinician. Such a test would save much tedious observation, would make earlier operation possible in the Stein-Leventhal syndrome, and would doubtless prevent many unnecessary operations. Thus far, detailed study of the urinary steroids has provided only a little evidence which might prove helpful. Gallagher<sup>20</sup> and Perloff<sup>18, 19</sup> and their associates have found a moderately elevated level of " $C_{19}O_2$ " steroids (androsterone, etiocholanolone, etc.) in the few cases studied. The  $C_{19}O_2$  compounds are presumably derived from strong androgen precursors such as testosterone and androstenedione. This finding lends support to our idea that the polyglandular syndrome is brought about by the production of too much androgen. They also observed, however, that the administration of prednisone ( $\Delta_1, 2$  cortisone) restored the level of  $C_{19}O_2$  steroids to normal in the cases studied. Since some of their patients were presumed to have the Stein-Leventhal syndrome, their results do not help much at present in providing a laboratory test for the selection of cases suitable for ovarian resection.

The fact that prednisone or analogous compounds suppressed the urinary excretion of  $C_{19}O_2$  steroids, as observed by both the Gallagher and Perloff groups, certainly lends support to the idea expressed by Du Toit<sup>10</sup> that the syndrome is produced by hyperadrenocorticism. If this were the correct explanation of all cases, however, how would one explain the beneficial effects of ovarian resection? The restoration of normal menstrual cycles in the cases which respond to resection is fully as dramatic as in cases of arrhenoblastoma subjected to operation. Certainly no one entertains the thought that there is adrenal dysfunction in the latter. Similarly, there is no suspicion that there is any primary ovarian dysfunction in cases of adrenal tumors. We believe,

therefore, that the bulk of the evidence indicates that resection of the medullary tissues of the ovary does not break a vicious circle in the polyglandular syndrome, as suggested by Du Toit, but rather that the resection removes tissue which produces androgen.

At the present time there is only a little evidence that the medullary tissue does produce an androgen. Holmstrom and his co-workers<sup>21</sup> have studied the ovary in one case. They have found that ovarian tissue removed by wedge resection in one case of the Stein-Leventhal syndrome behaves differently from normal ovaries when incubated with progesterone. When progesterone was incubated with normal ovarian tissue relatively large amounts of 17-alpha-hydroxyprogesterone and only traces of  $\Delta_4$ -androstenedione were produced. When progesterone was incubated with the Stein-Leventhal ovarian tissue, however, relatively large amounts of  $\Delta_4$ -androstenedione and only small amounts of 17-alpha-hydroxyprogesterone were produced. Similar findings on several Stein-Leventhal ovaries, especially the medullary tissue, would do much to confirm the idea that the medullary tissue can produce potent androgens.  $\Delta_4$ -androstenedione is an androgen with about the same activity as testosterone.<sup>22</sup> This compound would be expected to inhibit the elaboration of FSH by the pituitary in the same way as testosterone, and withdrawal of  $\Delta_4$ -androstenedione would be expected to release the pituitary so that normal gonadotrophic stimulation of the ovary could occur.

If this theory is tenable, we have to suppose that there is continuous production of pituitary LH (ICSH) in order for the medullary tissue to continue producing the supposed androgen. We also must suppose that the level of FSH is below the minimal amount necessary to produce maturation of the Graafian follicles and ovulation. In line with this, Keettel and his co-workers<sup>23</sup> have observed rapid enlargement of the ovaries in some cases of the Stein-Leventhal syndrome from the administration of FSH. This certainly suggests that these patients already had adequate levels of LH. In this connection Sherman and Woolf<sup>24</sup> are reporting the finding of higher than normal LH levels as well as abundant ovarian hilar Leydig cells in patients with endometrial cancer. They coincidentally observed LH levels in 6 patients with the Stein-Leventhal syndrome and noted that the LH levels were high normal or slightly elevated in all instances. These findings seem to be in general agreement with the proposal of Jackson and Dockerty<sup>25</sup> that endometrial cancer is more apt to occur in patients who presumably had an endocrinopathy similar to, if not identical with, the Stein-Leventhal syndrome. Of our 22 patients, however, 15 had had one or more uterine curettages. In no instance was there any frank or suggestive histological evidence of endometrial malignancy.

These theoretical considerations regarding the etiology of the syndrome leave much to be desired. In fact, we find ourselves with a theory which caused us to introduce the operation of medullary resection, an operation which has proved to be simple, safe, and satisfactory, yet we have only fragmentary evidence to support the theory.

### Summary

A surgical technique is described for the resection of the ovarian medulla. The procedure affords salvage in the treatment of the Stein-Leventhal syndrome at least equal to the salvage by other methods of ovarian resection. In addition, the procedure does not sacrifice large portions of ovarian cortex with its important complement of primordial follicles.

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## Discussion

DR. EDMUND W. OVERSTREET, San Francisco, Calif.—Like the rest of us, Dr. Allen struggles first with criteria for selection of patients, since adequate etiologic or pathologic definition of a disease entity is lacking. Stein himself includes only amenorrhea and sterility and insists that the fibrotically encapsulated, polycystic ovaries be definitely enlarged. By his criteria only about 50 per cent of patients have hirsutism, only about 20 per cent manifest obesity, and true virilism is notably absent. Yet 13 of Dr. Allen's 22 patients had definite hypertrophy of the clitoris and 6 had no enlargement of the ovary at all. Four cases combined both features, one admittedly an example of Sternberg's hilus-cell tumor. Current practice tends to include cases like these, largely on the basis of the ovarian histologic features. Thus Shippel, emphasizing the hyperthecosis, is led into an extraordinary gamut of clinical variation. While this tendency presents us with more patients, it seems further to obscure our view of the etiologic mechanisms.

Dr. Allen presents a carefully constructed argument for an ovarian source of excessive androgen production; and he relegates the adrenal to a bystander's role. There is, as he agrees, no direct proof of the former. Moreover, much evidence today suggests an active adrenal participation in a disturbed three-cornered relationship. But Dr. Allen's hypothesis does receive nice support from Dr. Ingersoll's report of an elevated LH (ICSH) excretion in 5 patients with the Stein-Leventhal syndrome. Its most striking and controversial feature, however, is that he designates as the androgen source, not the hyperplastic theca cells, but the Leydig cells of the ovary. To remove these, he has devised his technique of ovarian medullary resection.



But what does this sort of ovarian surgery actually do? Dr. Allen attacks the medulla with extensive resection. Bailey in England advocated complete extroversion of the ovaries without much regard to removal of tissue. Others excise large portions of thickened tunica and of cortex. Stein emphasizes puncture of the multiple cysts with as little tissue resection as possible. Yet in properly selected cases all of these methods give equally good results. What is their common denominator? To my mind, what they all accomplish is *trauma* of both ovaries—by whatever method of cutting or resecting. The suspicion is inescapable that *injury per se*, plus the subsequent healing processes, is the factor responsible for a depression of ovarian secretory function, which brings about a beneficial break in the limping ovarian-pituitary (and probably adrenal) relationship. I suspect that a sort of multiple Chinese acupuncture of the ovaries without any tissue removal would prove just as effective as wedge resection methods.

Finally, let me present an added puzzlement of my own. Stein has had opportunity to observe a number of patients' ovaries at laparotomy *after* earlier wedge resection. Similar scattered cases are reported by others. No recurrence of the Stein-Leventhal ovarian changes has ever been observed. I have 2 patients in whom perplexed surgeons had previously carried out ovarian biopsy amounting to ample wedge resection—of *one ovary only*. Pathologic description in one case and personal tissue review in the other proved the presence of typical Stein-Leventhal microscopic features. Moreover, both patients had a classical, *clinical* Stein-Leventhal syndrome when they later came under my care. At laparotomy I encountered superb examples of enlarged, typical, *bilateral*, Stein-Leventhal ovaries. My question is: What factors permit recurrence of the ovarian changes in a single ovary subjected to wedge resection, but apparently prevent their recurrence when both ovaries are thus traumatized?

DR. CONRAD G. COLLINS, New Orleans, La.—Broadly speaking, the author's paper contains two main facets. One is their theory stating "that for some reason, probably genetic in origin patients with the Stein-Leventhal syndrome have tissues in the medulla of the ovary which produce too much androgen." The second is a description of their technique for removal of this area or areas and the results attained.

In addition to this valuable presentation two recent comprehensive articles appearing in the continental literature (Bull. Soc. roy. belge de gynéc. et obst., vol. 27, No. 6, 1957) point to the continuous production of pituitary LH (ICSH) in order for the medullary tissue to continue to produce the supposed androgenic substance. There is agreement that the medulla in resected cases shows hyperplasia of the stromal cells and sometimes demonstrates luteinization of these stromal cells.

It is our purpose to add evidence to these contentions by demonstrating some of the cases of masculinizing ovarian tumors which have been observed on the Tulane Unit, Charity Hospital. At the same time it will be quite evident that, when dealing with the ovary, morphology does not always portend a specific biologic effect. All cases of hirsutism and/or masculinization of the female encountered on our service are studied by a team headed by Dr. John Weed of the department of Gynecology and Obstetrics, and Dr. William Sternberg, Professor of Pathology, both of Tulane University. In this manner comparatively many cases of masculinizing tumors have been well studied and those we present today represent but a few of the group needed to substantiate some ideas. The ideas are those of Dr. William Sternberg who has educated and converted me to his thoughts on the subject.

In one group of patients we have observed stromal hyperplasia in postmenopausal women, some areas diffuse and some distinctly nodular. In both areas luteinized or lutein-like cells were encountered. Near the hilum groups of similar-appearing cells, Leydig cells were found. Studies for dehydrogenase activity showed that in both areas intense metabolic processes were occurring. These two types of cells can be stimulated by the administration of chorionic gonadotropin. As a matter of fact, a mitotic figure was seen in a Leydig cell in one case. I am informed that this is rare and not encountered in the



testis or hilar cells of the ovary unless so stimulated. The patient from whom this ovary was removed had chorionic gonadotropin prior to operation. There was no masculinization in any of the women.

We now come to a group of women who exhibited typical signs and symptoms of masculinization of the female:

1. A woman in her eighties in whom a small hilar-cell tumor associated with marked stromal hyperplasia and luteinization was found (slides).
2. Two cases of theca-cell tumors associated with hilar-cell tumors and hilar-cell hyperplasia.
3. A pure theca-cell tumor in an ovary whose cortex is not unlike that found in the Stein-Leventhal syndrome.
4. A young woman with so-called "giant ovaries." Here we found ovaries not unlike those found in the Stein-Leventhal syndrome showing marked stromal hyperplasia and luteinization.

This group represents masculinization associated with hilar cells and stromal hyperplasia, masculinization with theca-cell tumor and hilar-cell tumor and, most important, marked masculinization associated with a pure theca-cell tumor. We believe this study by Dr. Sternberg adds credence to the thoughts of the authors relevant to the underlying physiopathologic changes found in this syndrome. Certainly Dr. Ingersoll's biologic studies add much weight to this concept.

The last case we wish to present demonstrates the concurrent presence of a hilar-cell tumor and granulosa-cell tumor in a woman with masculinization, and shows how difficult it would be to remove hilar cells short of oophorectomy, especially if hyperplasia of these cells and not a discrete tumor was found.

All these findings point to excess secretion of an androgenic substance from the stromal cells as the probable cause of the Stein-Leventhal syndrome. The results attained by wedge resection of the ovary or medullary resection are also clarified.

Yet to be explained, however, are the published results obtained by the methods of decortication of the ovary or simple bisection with suture of cortical surface to cortical surface.

DR. JAMES L. REYCRAFT, Cleveland, Ohio.—The gynecologist who is primarily a clinician is frequently confronted with problems bearing on ovarian dysfunction. Among patients who complain of scanty menstruation or amenorrhea, a certain number are found to have what is now referred to as the Stein-Leventhal syndrome.

In 1937, before this Society, I presented 6 cases in a paper entitled "Surgical Treatment of Ovarian Dysfunction," all treated surgically, inasmuch as they had not responded to endocrine therapy. In 1948, I reported 11 additional, and I now have 10 more such cases, all from my private practice.

In the group of 11 cases reported upon in 1948, a justifiable criticism by Dr. Emil Novak was that 2 of the cases proved to be theca-cell tumors, and one was a case of Chiari's syndrome. Five of the remaining 8 patients have become pregnant at least once since that time.

More recently we have modified the operative procedure in that, while we usually do a wedge resection (if the ovary is large), we now use a Gelfoam "patch" over the denuded area in the event that we have employed only partial decortication. The latter procedure controls bleeding and may lessen the incidence of omental adhesions.

We have not employed culdoscopy or pneumoperitoneum as a diagnostic aid. It is our opinion that we can usually make the diagnosis by the history and a careful bimanual pelvic examination.

You will be impressed with the fact that we have been very conservative in choosing cases for operation. In the past 11 years I have operated upon just 10 such cases from my private practice. I wish to report, however, that 9 of the 10 patients have become

pregnant at least once since the operation; seventeen children have been born and two more are due within a few weeks from now. The only patient who has not conceived has a husband who has been proved to be sterile.

DR. ALLEN (Closing).—I have to confess, of course, that the reason for presenting the theory regarding the rationale for medullary resection is to encourage detailed study of the endocrine dysfunction present in these patients. With the newer methods now available it should be possible to prove or disprove the theory which we have proposed.

One additional comment in accord with Dr. Ingersoll's paper needs to be made. If we are correct in assuming that the ovaries produce an excess of androgens in these cases, the pituitary gland must produce adequate amounts of LH. Ovulation should then occur if there were adequate amounts of FSH. Since ovulation seldom occurs, one might predict that the FSH levels in these patients would be lower than normal. The literature reveals that the FSH is not elevated in these patients. Occasionally, as was pointed out in a slide by Dr. Keettel yesterday, the FSH may, in fact, be a little low. As a matter of fact, Keettel himself has shown that if you give these patients FSH, the ovaries respond by getting even larger in much the same way as the augmentation reaction is carried out in measuring FSH when an animal is given plenty of chorionic gonadotropin, a variety of LH, and then FSH is added to it.

## A POSITIVE CYTOLOGY REGISTRY: ITS USEFULNESS IN THE DIAGNOSIS AND MANAGEMENT OF CANCER\*†

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THIS is a progress report of the observations we are making on genital cancer with the assistance of a Positive Cytology Registry. All of the data used were accumulated with the assistance of this Registry. This approach might be slightly different from that employed elsewhere, thus providing another perspective of cytology in obstetrics and gynecology. The distinctiveness of the method lies in our intense pursuit of every woman who has been found to have exfoliated cancer cells in the cytological smear. With almost equal vigor we are able to follow women who show atypical cells but who do not qualify for our Positive Cytology Registry.

We define "positive cytology" as smears that contain cancer cells or cells that are suspected of being cancer cells. All of the smears that qualify our patients for matriculation in the Registry fit into Papanicolaou's Classes III, IV, and V.

The structure and functions of the Positive Cytology Registry are described in greater detail elsewhere.<sup>1</sup> At present the Registry staff consists of two women whose activities are a combination of clerical and medical social work. They assemble and act as custodians of all information pertinent to the patients and their cytologic records. These workers establish a close, personal follow-up of patients in whom we are interested. Great efforts are made to see that these patients return for the indicated studies.

A matriculate in the Registry has a cytologic examination at every clinic visit, every hospital admission, and every visit to the emergency room. With these complete records we are evaluating the use of cytology in the follow-up of the patient treated for cancer as well as seeking the meaning of positive cytology in the woman who has not been proved to have cancer. This study of our matriculates, coupled with the smears we obtain on all of our patients, is providing us with valuable information on the history of the exfoliation of normal and abnormal cells in many individuals.

In addition to their research function the Registry workers provide valuable services for the patients. They attempt to have each patient understand

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her problem and they explain the need for repeated examinations. Return visits are facilitated for the patients in a way that only sympathetic and knowledgeable case workers can provide. When patients become ineligible for free care or move to another region, physicians and hospitals are provided with case records. The Registry maintains contact with the patients through their new physicians. All of the patients were originally, at least, "staff" ("clinic") patients who were eligible for free (or nearly free) care at the Jackson Memorial Hospital.

### A Chronicle of the Registry

As of July 1, 1958, there were 443 women matriculated in the Positive Cytology Registry. This is the yield from approximately 19,000 examinations (36,000 slides). There has been a steady increase in the number of cytology examinations. In the first half of 1958, 4,000 examinations were completed. The presence of the Registry, with its ability to provide continuity in the observation of patients, has encouraged all members of the department in the growth of our cytology program.

Almost all of the 443 cases have been collected since cervical cytologic examinations became a routine in 1952 on patients admitted to the Gynecology Out-Patient Clinic. A small number are from earlier years. The following lists progressively the steps in the subsequent development of our cytology services to patients:

1. November, 1955. All new admissions to the antepartum clinics.
2. November, 1955. All patients returning for their first postpartum visit.
3. July, 1956. The establishment of the Positive Cytology Registry with the part-time assistance of several workers in the department.
4. July, 1956. All staff patients of other departments seen by us in consultation. This is approximately 600 patients a year.
5. January, 1957. All patients seen in emergency room by members of the department, if a recent cytology report is not in the patient's record. We are averaging 30 cytology examinations a week from this source of patients.
6. April, 1957. Support of the Registry by the National Cancer Institute began. Provided for two full-time workers.
7. January, 1958. Patients admitted to the labor-delivery unit who have not had antepartum care.

*Cytology Studies in Labor-Delivery Unit.*—We have approximately 600 staff patients a year delivered who have received no antepartum care. This is the type of patient who would be likely to have gone for long periods of time without a pelvic examination and cytology examination.

This portion of the program began with exploration into the best and most practical manner of obtaining good smears on women admitted to a labor-delivery unit. We already had some experience in making smears under these conditions in our work in the cytodetection of ruptured amnion.<sup>2, 3</sup> Methods tried were: with and without placing the patient's feet in stirrups; with and without a speculum; with our conventional wooden spatula rubbed over the cervix; and with a piece of gauze placed over the rubber-gloved hand and gently drawn over the cervix. It was learned that the simplest method produced just as satisfactory a smear as any other technique. Now, without a speculum and without the feet placed in stirrups, the fingers of the gloved hand are wiped across the cervix and the material on the finger tips is smeared on glass slides. Naturally, patients with completely dilated cervixes on admission, patients bleeding or exhibiting other emergency conditions are



excluded in favor of more pressing attentions. One hundred and forty-six cytology studies were done in the first 6 months of 1958 and 2 cases of cancer of the cervix were found.

In the future the cytology work in the above areas can be separately analyzed to determine the effectiveness of each portion of our program.

### Basic Data

Each cytologic study is started by insertion of the unlubricated speculum into the vagina and scraping the cervix twice with separate wooden spatulas. An attempt is made to reach as far as possible into the endocervical canal. Two slides are smeared at each study.

*Race.*—Fifty-two per cent of the patients in the Registry are Negroes. As 54 per cent of the patients attending the outpatient clinics of the Department are Negroes, the racial distribution of positive cytology needs no special comment.

*Length of Follow-up.*—The completeness of our follow-up can be seen in Table I, wherein the patients are listed according to the year of their most recent pelvic examination and cytology study. Fifty-eight per cent of the patients were seen in the first 6 months of 1958 and 95 per cent in the 18 months that preceded July 1, 1958.

TABLE I. YEAR OF LAST EXAMINATION OF ALL WOMEN IN POSITIVE CYTOLOGY REGISTRY

YEAR	NO. OF PATIENTS
1958 (first 6 months)	212
1957	158
1956	11
1955 and earlier	13
Died	49
Total	443

*Chief Diagnoses.*—The chief diagnoses in all of the cases in the Registry are given in Table II. The most common diagnosis was cervicitis with 137 cases, closely followed by invasive cancer of the cervix with 130 cases. Most of the 60 patients who had no tissue diagnosis represent earlier and lost-to-follow-up cases, patients who have moved away or are no longer under our care. There were 59 cases of intraepithelial carcinoma of the cervix and 38 with basal-cell hyperplasia.

TABLE II. CHIEF DIAGNOSES OF ALL WOMEN IN POSITIVE CYTOLOGY REGISTRY

DIAGNOSIS	NO. PATIENTS
Invasive carcinoma of cervix	130
Intraepithelial carcinoma of cervix	59
Basal-cell hyperplasia	38
Cervicitis	137
Carcinoma of endometrium	13
Carcinoma of vulva and vagina	2
No tissue diagnosis	60
Carcinoma of ovary	2
Cervical polyp	2
Total	443

Intraepithelial carcinoma of the cervix (in situ) is diagnosed when the characteristic cellular abnormalities are present in the entire thickness of the epithelium. These characteristics are the conventional ones of altered polarity

with the long cell axis tending to be vertical, pleomorphism, deeply staining nuclei, and an increase in mitosis, which is not confined to the lower portion of the epithelium. We are not making this diagnosis by cytology.

Basal-cell hyperplasia as used in this report encompasses a number of diagnoses that were used to describe tissue of patients in this hospital. Among these diagnoses were "atypical epithelium," "atypical hyperplasia," "dysplasia," and "basal cell hyperplasia." Basal-cell hyperplasia is employed in this report because it was the term used most frequently. All of these diagnoses were similar in that they were borderline lesions, often with lesser degrees of epithelial atypicality than in intraepithelial carcinoma, and did not include the entire thickness of the epithelium.

*Carcinoma of the Endometrium.*—The smears of the 13 women in the Registry with carcinoma of the endometrium were made by our usual cervical surface scraping technique. In the last 59 cases of carcinoma of the endometrium at the Jackson Memorial Hospital (both private and staff cases) 48 per cent had positive cytology.<sup>4</sup>

*Deceased Patients.*—Of the 49 deceased patients (Table III) the cause of death was proved to be cancer of the uterus in 29 instances: 27 had cancer of the cervix; 2, cancer of the endometrium; and in 1 the origin in the uterus could not be determined.

TABLE III. CAUSES OF DEATH IN 49 PATIENTS IN POSITIVE CYTOLOGY REGISTRY

DIAGNOSIS	NO. PATIENTS
Cancer of cervix	27
Cancer of ovary	1
Cancer of endometrium	2
Cancer elsewhere (all stomach)	3
Medical disease unrelated to cancer	10
Cancer of unknown origin	1
Unknown causes	5
Total	49

*Age.*—The ages of the women in the Registry ranged from 14 to 84 years with a median of 37 years. The need to include all women regardless of age in cytologic surveys is supported by our learning that 31 per cent of our patients with positive cytology were 29 years of age or younger.

The median age of patients with basal-cell hyperplasia was 29 years at the time of the diagnosis. The median age for intraepithelial carcinoma was 35 years and for invasive cancer, 46 years. This fits rather too neatly into the concept that basal-cell hyperplasia is a precursor of intraepithelial carcinoma, which in turn is a precursor of invasive carcinoma.

*Nulligravidas With Positive Cytology.*—The Registry is not large enough yet to seek a relationship among the various diagnoses and many of the factors which have attracted attention in the epidemiology of uterine cancer such as number of pregnancies, age at the various pregnancies, type of obstetric care, and sexual history. A significant remark can be made about the number of women who were never pregnant. Among the 443 patients in the Registry there were 30 nulligravidas (7 per cent). For controls the records of 350 unselected women of 16 years of age and over who attend the Medical Out-Patient Department were examined and 16 per cent found to be nulligravidas. Provided these controls are valid, the probability of this difference in the percentage of nulligravidas in the two classes of women occurring by chance is less than 1 to 1,000.

*Cytology for Primary Detection of Cancer.*—Because of the source of our patients, our experience with cytology does not serve well to estimate the usefulness of the smear in the primary detection of neoplastic disease in healthy women. Nevertheless, even among the 409 matriculates who had a recorded observation of the cervix at their first examination, we can note that only 55 per cent had a visible lesion on the cervix. In Table IV, where the diagnoses are listed with the percentage of patients with each diagnosis who had visible lesions, it can be seen that the prevalence of a visible lesion decreased *pari passu* with the decrease in the severity of the cervical disease.

TABLE IV. COMPARISON OF DIAGNOSES AND THE PERCENTAGE OF WOMEN IN EACH DIAGNOSIS WHO HAD VISIBLE LESION ON CERVIX

DIAGNOSIS	% WITH CERVICAL LESION
Invasive carcinoma of cervix	81
Intraepithelial carcinoma of cervix	69
Basal-cell hyperplasia	61
Cervicitis	46
Carcinoma of endometrium	23

*Cytologic History Before Discovery of Positive Cytology.*—An attempt was made to construct the history of cellular exfoliation in our patients before the appearance of positive cytology. Quantitatively, the data were inadequate. It is apparent that the Registry will have to be in existence longer before meaningful data on the deterioration from negative smears to positive smears and on the events associated with this change can be collated.

The same quantitative inadequacy was found when the records were searched for cases in which there was an interval of more than one year between the discovery of positive cytology and the diagnosis of cancer.

#### **Patients With a Regression From Positive to Negative Cytology ("Spontaneous Disappearance")**

We have been particularly interested in a group of 118 women who had what we refer to as "spontaneous disappearance" of positive cytology. The term "spontaneous disappearance" is admittedly a poor one, especially as the persistence with which we examined these women with punch and cone biopsies permitted little spontaneity. The ability of our diagnostic work to eradicate abnormal tissue will be demonstrated later. Other descriptions that might be used are "spontaneous regression," "unconfirmed positives," or even the label "false positives." Women who were pregnant at the time of their first positive cytology are excluded from this section of our report.

These women changed from positive to negative cytology without radiotherapy, hysterectomy, or excision of the cervical stump. The conviction that a more complete understanding of this group of women will be a valuable contribution in cytology and genital cancer is responsible for our interest. A possibility is that a temporary exfoliation of cancer cells, a trait that the body was able to overcome at the moment, may indicate a biologic susceptibility to cancer in the uterus, or elsewhere in the body; on the other hand, it might be interpreted as increased host resistance. The continued observation of this growing group of patients over a number of years may produce an answer to these questions raised.

The length of the follow-up in these patients appears to be substantial enough to recognize that a bona fide alteration in cytology is being reported. Among the 118 women in the spontaneous disappearance category, the interval of time of follow-up from the date of the first positive cytologic examination to the last negative one ranges from one month to 7 years and 3 months, with

a median time of 2 years and 7 months. This follow-up interval is 4 or more years in 24 per cent of these patients, 3 or more years in 41 per cent, and less than one year in only 17 per cent.

Thirteen of these women were found to have positive cytology twice, 9 had it on three occasions, and 2 had it on four separate studies before the change to negative appeared. These repetitions of positive smears enforce our confidence in the earlier presence of the exfoliation of cancer cells.

The chief diagnoses in the 118 spontaneous disappearance cases are listed in Table V. Cervicitis was the most frequent diagnosis (74 patients). Too

TABLE V. CHIEF DIAGNOSES IN 118 SPONTANEOUS DISAPPEARANCE CASES

DIAGNOSIS	NO. PATIENTS
Invasive carcinoma of cervix	1
Intraepithelial carcinoma of cervix	3
Basal-cell hyperplasia	15
Cervicitis	74
No tissue diagnosis	23
Cervical polyp	2
Total	118

many women had no tissue diagnosis (23 patients) and an explanation of this deficiency has been made above. Fifteen had basal-cell hyperplasia. Three women had intraepithelial carcinoma and elected not to have a hysterectomy. Two women had a benign cervical polyp excised between the positive and the subsequent negative smears. The one case of invasive carcinoma proved to be a false negative, the lesion failing to exfoliate cancer cells.

The treatments and diagnostic studies used in these 118 spontaneous disappearance cases are given in Table VI. Thirty-three had no treatment or

TABLE VI. TREATMENTS AND DIAGNOSTIC STUDIES IN 118 CASES OF SPONTANEOUS DISAPPEARANCE OF POSITIVE CYTOLOGY

TREATMENT OR STUDY	NO. PATIENTS
Conization biopsy	50
Punch biopsy	30
Excision polyp	2
Dilatation and curettage only	1
Cauterization only	1
Amputation of cervix	1
None	33
Total	118

diagnostic work that we associate with ablation of diseased uterine tissue. The remainder all had procedures that may have been responsible for the disappearance of the abnormal cells. Fifty had cone biopsies. Most of our puzzling cases with positive cytology now have a conization to obtain a large specimen for biopsy. All have cytology examinations repeated at least yearly. The possibility of the treatment of vaginitis assisting in the reversal of the cytology smear in these patients has to be considered. To date we have not measured the effect of the treatment of vaginitis in our patients.

The patients in our spontaneous disappearance group tended to be younger women. Their median age was 31 years at the time of the first positive cytology, younger than the median age for all women in the Registry (37 years), slightly lower than that of the women with intraepithelial carcinoma (35 years) and considerably younger than those with invasive carcinoma of the cervix (46 years).



As every large number of women examined cytologically includes false positives, undoubtedly our false positives lie in this spontaneous disappearance group of patients. Perhaps everyone's false positives, unless plainly a misinterpretation of the smear due to inexperience, deserve close observation for many years. In comparing our experience with that of others it should be noted that our definition of positive cytology includes a wider range of smears than some writers use. We include Papanicolaou Class III in our positive group. Others have recorded Class III as "suspicious" or have assigned some other designation and have only the more alarming Classes IV and V as positive cytology. It seemed to us that our Registry would be more useful by including Class III. We can report here that a large percentage of our spontaneous disappearance cases had only Class III smears (Table VII), the least of the three positive classes.

TABLE VII. DISTRIBUTION OF THE DIFFERENT PAPANICOLAOU CLASSES AMONG WOMEN IN REGISTRY WITH SPONTANEOUS DISAPPEARANCE, BASAL CELL HYPERPLASIA, INTRAEPITHELIAL CARCINOMA, AND INVASIVE CARCINOMA OF CERVIX

	PAPANICOLAOU CLASS %		
	III	IV	V
Spontaneous disappearance	51	38	11
Basal-cell hyperplasia	27	47	26
Intraepithelial carcinoma	33	44	23
Invasive carcinoma	16	38	46

Table VII compares the degree of abnormality of the smears among the spontaneous disappearance cases and patients proved to have basal-cell hyperplasia, intraepithelial carcinoma, and invasive cancer. As anticipated, a majority in the spontaneous disappearance group had only Class III slides, while invasive cancer had a preponderance of Class V. The Class V slide, however, was represented among the spontaneous disappearance cases (11 per cent) and Class III was found among the invasive cancer cases (16 per cent). A safe conclusion that may be drawn from this is that the degree of positiveness cannot be used as an indication of what management is needed or as a measure of the urgency. Any positive cytology report merits a conscientious investigation.

In Table VII it can be noted that basal-cell hyperplasia and intraepithelial carcinoma were decidedly alike in their exfoliation of these abnormal cells.

#### Excision of Cervical Tissue for Biopsy by Conization

As excisions of cervical tissue for biopsy were done in so many cases of spontaneous disappearance of positive cytology, we can consider these procedures at this point. It has been shown in Table VI that 50 of these 118 women had cone biopsies and 30 had punch biopsies. Some of these women had punch biopsies done several times. Our punch biopsies are quadrant biopsies and any visible lesion is sampled. Six patients had conization done twice.

The ability of the punch biopsy to remove abnormal tissue from a cervix in some cases is illustrated by the following data. In the last 4 years there have been 213 diagnostic conizations done on staff patients at the Jackson Memorial Hospital. One hundred and fifty-four of these women had a punch biopsy performed at least once before the conization, and 19 of them showed that the original lesion found by punch biopsy was not present in the cone specimen. Cervicitis was the only diagnosis that could be made on the cone in 12 women who originally had basal-cell hyperplasia, 5 women who had intraepithelial carcinoma, and 2 women who had invasive carcinoma of the cervix.

Eighty-nine of the 213 women who had conizations eventually had hysterectomies. The competence of the conization operation in removing

diseased tissue is summarized in Tables VIII and IX, which show that 58 women had complete removal of the lesion or a less serious one remained on the uterus. Forty-three women had intraepithelial carcinoma completely removed by the conization, 8 had basal-cell hyperplasia removed, and 2 had no evidence of invasive carcinoma remaining in the uterus. After conization, basal-cell hyperplasia was all that could be found left in the uterus in 4 women who had shown intraepithelial carcinoma and in one woman who had invasive cancer in the cone.

TABLE VIII. COMPARISON OF DIAGNOSIS ON CONIZATION AND HYSTERECTOMY SPECIMENS

More serious lesion on uterus than on cone	8
Same lesion on uterus as on cone	23
Less serious lesion on uterus than on cone	58
Total	89

TABLE IX. COMPARISON OF DIAGNOSES ON CONIZATION AND HYSTERECTOMY SPECIMENS IN 58 PATIENTS WITH LESS SERIOUS LESION ON THE UTERUS THAN ON THE CERVIX

CONIZATION SPECIMEN	HYSTERECTOMY SPECIMEN
Intraepithelial carcinoma of cervix	Cervicitis 43
Intraepithelial carcinoma of cervix	Basal-cell hyperplasia 4
Basal-cell hyperplasia	Cervicitis 8
Invasive carcinoma of cervix	Basal-cell hyperplasia 1
Invasive carcinoma of cervix	Cervicitis 2
Total	58

Twenty-three women had the same lesion in the hysterectomy specimen as in the cone. Among these were 9 cases of cervicitis, 2 of basal-cell hyperplasia, and 12 of intraepithelial carcinoma. These women, and a group of 8 women who had a more serious lesion in the uterus than in the cone, demonstrate the risk in assuming too readily that conization has removed all of the neoplastic tissue. After the accumulation of more cases we will be able to report on the efficacy of cytology in deciding when conization has been adequate treatment. Some of the cases discussed in this paragraph come from the earliest experience with conization in the hospital. The amount of tissue removed by conization has increased, and with it we hope that fewer lesions remain in the uterus.

It is possible that these comparisons between the cone and the specimen resulting from hysterectomy might be slightly different if the cone specimen and the remaining cervical tissue on the uterus were serially sectioned. Serial sectioning as a routine is impractical. Our present plan is to make 12 tissue blocks from the cone and step sections from each block. More sections are made when indicated, for example, when there are unexplained positive cytologic findings or a perplexing histologic pattern.

Some discrepancies among punch, cone, and hysterectomy specimens may be accounted for by an abrasion of the epithelium at the several vaginal examinations that these patients inevitably have. Our present technique of conization is designed to avoid this type of loss of important tissue but it may be impossible to eliminate the other occasions. The following are the essential steps in our conization operation: general or spinal anesthesia; no vaginal preparation; 7 per cent tincture of iodine sprayed on the ectocervix; epinephrine-saline solution injected into the cervix; excision of specimen before dilatation; cold knife for excision; specimen includes in one piece all of the squamocolumnar junction and all of the ectocervix that appears abnormal or that does not take the iodine stain well; specimen includes at least 1.5 cm. of the endocervical canal, usually now 2 cm. in the fresh specimen; minimum

handling of the cone; curettage of any remaining endocervical canal with a small, sharp curette; dilatation of the internal os; and curettage of the uterine cavity.

One hundred and sixty-one women had additional tissue removed at the time of conization as a result of this fractional curettage. In only 3 was malignant tissue obtained that was not found in the cone; 2 of these had adenocarcinoma of the endometrium and one had intraepithelial carcinoma of the remaining endocervical tissue.

### Conization in Pregnancy

As we know that in many localities there is a reluctance to proceed with a cone biopsy during pregnancy, our experience with this operation in 13 women will be described.

Indications for conization in pregnancy have been the same as in non-pregnant women. In 3 cases the significant preceding event in the pregnancy was the diagnosis of intraepithelial carcinoma on punch biopsy; in 3 other cases punch biopsy had shown a basal-cell hyperplasia; in 6 instances the conization was done because of positive cytology. One patient had a conization because 4 months earlier she had had a first conization with a diagnosis of intraepithelial carcinoma; she became pregnant and continued to have positive cytology. The diagnosis on her second conization was basal-cell hyperplasia.

The weeks of gestation in which these operations were performed are: 8, 8, 8, 9, 9, 10, 14, 18, 22, 28, 29, 33 and 38. It might be considered that 6 were performed in the first trimester, 3 in the middle trimester, and 4 in the last trimester.

The diagnoses obtained after conizations in these pregnant patients were: intraepithelial carcinoma of the cervix, 7; basal-cell hyperplasia, 4; invasive cancer, 1; and cervicitis, 1. The question of whether conization in pregnancy is justified might be answered by consideration of these diagnoses. Was the acquisition of the exact diagnosis in these cases important? Without a cone to examine could we have been sure that they did not have invasive cancer?

The operation in pregnancy is essentially the same as in the nonpregnant woman. Naturally, dilatation of the internal os and curettage are omitted. The injection of an epinephrine-saline solution into the cervix permits the operator to excise deliberately a cone specimen of the same size and shape as in the nonpregnant. Large bleeding vessels are touched with a suction-cautery instrument. Sutures are usually not needed. A 1 inch plain gauze pack, with or without Gelfoam, is sometimes inserted into the defect for 24 hours. There have been no cases with immediate or delayed postoperative hemorrhage. Some of the patients receive more postoperative sedation than the average postconization patient. No hormones are administered. No abortions have been caused.

**Complications.**—One operation, done in the eighth week of pregnancy, was marred by a perforation of the uterus at the junction of the cervix and the corpus, without entering the uterine cavity. The patient had an uneventful delivery of a 2,325 gram infant in the thirty-seventh week of pregnancy.

One patient had a very minor laceration of the cervix at delivery. Another woman had a severe laceration at delivery and her history is as follows:

M. R. had basal-cell hyperplasia diagnosed on two occasions by punch biopsy before the pregnancy under consideration. The biopsies were done because she had a lesion on the cervix and positive cytology. After the punch biopsies the cytology became negative.



The cervix and a widely everted endocervical canal were cauterized, perhaps injudiciously, on four occasions. When she subsequently became pregnant she developed a large cauliflower lesion in the endocervical canal that had to be considered malignant, although her cytology was negative. A cone specimen was excised in the eighteenth week of pregnancy and only basal-cell hyperplasia found. At term she was in good labor for 26 hours and there was only enough dilatation of a very firm internal os to admit a finger tip. This os was stretched gently and promptly expanded, or lacerated, to 5 cm. dilatation. In one and a half hours she was delivered of a 3,685 gram infant in good condition. Two massive cervical lacerations caused profuse hemorrhage and shock. The lacerations were repaired and the patient made an uneventful recovery. We do not know whether or not the scar tissue at the internal os and the lacerations were the result of the cauterization or the conization.

*Prematurity.*—It is impossible at the present to say there is an association between premature delivery and conization. The number of cases permits only general observations. Seven of the 10 women delivered had premature babies (2,500 gram or less). Two have not been delivered at the time of this writing. One woman had a missed abortion which was more likely due to the removal of a large corpus luteum cyst through a posterior colpotomy; this was done at the time of the conization in the ninth week of pregnancy. The uterus, with the missed abortion and an intraepithelial carcinoma of the cervix, was removed 4 months later.

The average weight of the 7 premature babies was 2,138 grams, which is not extraordinary when it is considered that 6 of the 7 were Negroes and that the incidence of premature delivery among staff patients at this hospital is 14.4 per cent.

Also making it difficult to evaluate the relationship between the conization and premature labor is the observation that 6 of the 7 mothers who had a conization and a premature baby had had at least one premature baby in earlier pregnancies. Not clarifying the question is the case of the mother who had a mature baby after conization and who had a history of 4 premature infants in preceding pregnancies.

All of the premature infants survived except 2, and each death might conceivably be considered a result of the conization operation. In both cases the final diagnosis was intraepithelial carcinoma:

1. R. L. had a conization in the eighth week of gestation. In the thirty-fourth week of pregnancy she was admitted to the hospital with a pulsating cord prolapsed through an undilated cervix. A premature infant was promptly delivered by cesarean section but was stillborn.

2. H. A. had a conization at 33 weeks. Due to some lamentable accidents with the tissue, invasion had not been excluded and was being seriously considered when she went into labor two weeks later. The premature infant died in the neonatal period after a cesarean section.

### Positive Cytology in Pregnancy

Of the 443 patients in the Registry, 34 were pregnant at the time of their first positive cytology. These pregnant patients have been excluded from some of the earlier discussions in the paper because of the uncertainty present in many minds as to the effect of pregnancy on the exfoliation of abnormal cells.

Five of these 34 women had negative cytology studies before they were pregnant. The interval of time between the negative report and the positive one ranged from 2 to 23 months. Although this suggests a correlation between pregnancy and the appearance of positive cytology, the number of



patients we have in our Registry who had cytology studies before a positive one was found in pregnancy is not large enough to make valid observations. As our record of exfoliation of cells in many individuals grows, we will be able to make more comparisons on cytology before and during pregnancy in the same individual.

Contributing to the number of pregnant women with positive cytology, and distorting the picture, is the fact that at the Jackson Memorial Hospital we are dealing with a group of women who tend to have no pelvic examinations (and no cytology studies) except when pregnant. The cervix may have been exfoliating positive cells for some time before the pregnancy.

Another selective factor that has to be weighed is the motivation that brings a patient to the clinic or hospital emergency room. Women come to our gynecology clinic because they have genital complaints, including symptoms of cancer; hence they are more likely to have positive cytology. Women come to our antepartum clinic principally because they are pregnant, although undoubtedly if they sense an abnormality some are more likely to come to the hospital for antepartum care.

Supporting the increased likelihood of women with a disease producing positive cytology arriving in a gynecology clinic is the following spot check. In the last 1,000 gynecology patient studies the prevalence of positive cytology was 4 per cent; in the same period of time there were 667 antepartum patients who had cytology studies with a positive cytology prevalence of only 0.3 per cent. In these two groups it is consistent that we should find Papanicolaou Class II (atypical cells) in 16 per cent of the gynecology patients and in only 7 per cent of the antepartum patients.

In an earlier report,<sup>1</sup> when we had 21 of this type of women in the Registry, the patients were analyzed more closely than at this time. We concluded that positive cytology deserved the same attention in pregnant women as in nonpregnant women. Our data were not sufficiently large to determine whether or not pregnancy was an important inciter of positive cytology, or even whether it possessed that attribute. We have not yet collected conclusive information on the disappearance or retention of positive cytology after pregnancy is over. We possibly will not be able to make a contribution in this direction unless we abandon our strenuous plan of diagnostic studies which, as we have demonstrated, can be curative, at least temporarily.

Of the 34 patients who were first found to have positive cytology while pregnant, 23 have been adequately followed up. Thirteen of these 23 cases were negative after the pregnancy—but 6 had punch biopsies and 2 had conizations during the pregnancy. This leaves 5 with unexplained reversals to negative cytology. Ten cases remain positive despite the fact that 7 had punch biopsies and one had a cone biopsy.

TABLE X. DIAGNOSES OF PATIENTS PREGNANT AT TIME OF FIRST POSITIVE CYTOLOGY

Invasive carcinoma of cervix	2
Intraepithelial carcinoma of cervix	9
Basal-cell hyperplasia	8
Cervicitis	6
No tissue diagnosis	9
Total	34

The diagnoses among the 34 pregnant positive-cytology patients are given in Table X. Nine patients (26 per cent) had intraepithelial carcinoma of the cervix. It may be tempting for some to compare this with a 12 per cent prevalence of intraepithelial carcinoma among the nonpregnant and interpret

from it that pregnancy is responsible for the intraepithelial carcinoma, but the number of variables and the size of the samples make comparison invalid.

Greene and Peckham<sup>5</sup> reported that 8 of 37 intraepithelial carcinomas diagnosed during pregnancy could not be found after pregnancy. They also noted the loss of this diagnosis in nonpregnant women. Obviously these patients had at least punch biopsies.

Of our 9 patients with intraepithelial carcinoma in pregnancy, 3 were found still to have intraepithelial carcinoma 12 or more weeks after pregnancy; these 3 patients had only punch biopsies because they came before we grew bold with the conization in pregnancy. The remaining 6 did not have intraepithelial carcinoma when they had hysterectomy at least 12 weeks later; however, each of the patients had a conization as part of her diagnostic study. Thus our diagnostic studies have wiped away the opportunity for intraepithelial carcinoma to disappear spontaneously after the pregnancy, if it possesses that quality.

### Summary

Our Positive Cytology Registry is an organization that maintains follow-up on all of the staff patients in our hospital who have had positive cytologic examinations. Adjunctive services of the Registry lie in health education of the patient, maintenance of all cytology records, and acquisition of as complete a history of exfoliative cytology as possible in each patient. From about 19,000 examinations we have 443 women with positive cytology. Ninety-five per cent of these women have had a completed follow-up within a reasonable time of this report. Included in the expansion of cytology service and investigation is the obtaining of smears from women without antepartum care who are admitted to the labor-delivery unit; a successful and simple technique of making smears in these cases has been found. The most common diagnoses in the Registry are cervicitis and invasive carcinoma of the cervix. Some comparisons in age, exfoliation of cells, and nulligravidity are made among patients with invasive carcinoma of the cervix, intraepithelial carcinoma of the cervix, basal-cell hyperplasia, and those not proved to have cancer.

One hundred and eighteen women who lost this positive cytology without radiotherapy or hysterectomy are analyzed and the effect of diagnostic studies on the cervix noted. In particular, the effect of our technique of conization is related.

Experience in excising a large cone specimen during pregnancy in 13 women is recounted. Complications which may occur as a result of this operation, in particular premature delivery, are discussed.

Thirty-four women had positive cytology first found during pregnancy. Final opinion as to the relationship of pregnancy to exfoliation of abnormal cells and intraepithelial carcinoma of the cervix cannot be offered.

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### Discussion

DR. C. GORDON JOHNSON, New Orleans, La.—The value of a registry to keep adequate records of positive or suspicious smears has been demonstrated by groups such as those in Toledo and Lucas Counties, San Diego County, the University Hospitals of Cleveland, and many others. Their main purpose has been to record pertinent data and to maintain contact with such patients for adequate follow-up.

Dr. Ferguson's Positive Cytology Registry is a welcome addition to the ever-growing list. His particular interest seems to be the determination of what happened to a group of his patients who had a regression from positive to negative cytology. My impression of this group of 118 women appears to be that, of 95 with tissue diagnosis, in only 4 did this confirm the cytologic diagnosis of malignant or suspicious cells. I would consider the remaining 91 cases to represent false positives.

I am in complete agreement with Dr. Ferguson concerning the handling of pregnant patients with positive cytology.

For the past 3 years we have been fortunate in having the full-time services of an exceptionally well-trained cytologist in the Department of Gynecology and Obstetrics at the Browne-McHardy Clinic. I will briefly report our experiences during that period:

The majority of the patients examined cytologically have been referred from the medical department for a routine pelvic examination. In most instances there have been no gynecological symptoms. We obtain smears by the aspiration technique. All positive or suspicious smears are repeated and then followed by an adequate cold knife cervical cone and curettement.

We maintain a Registry that keeps a permanent record of all patients' cytological findings. The pathology report on cervical cones of suspicious or positive smears and further treatment of these cases is recorded. Patients in this category are notified when to return for follow-up smears.

Our Registry also keeps records for many doctors not associated with the clinic who send smears to our cytologist for interpretation.

From September, 1955, through May, 1958, we have screened 2,407 patients, 27 of whom had positive or suspicious smears. Papanicolaou Classes III, IV, and V comprise these positive or suspicious smears.

Positive smears were verified by histological examination in 20 cases. There were 9 cases of invasive squamous-cell carcinoma, 2 unsuspected. There were 9 cases of carcinoma in situ, all unsuspected. There were 2 cases of endometrial adenocarcinoma, both suspected.

Six suspicious smears, all Class III, were not verified by histological examination. Four of these contained cells that were suspicious of endometrial adenocarcinoma. One patient refused conization and has been lost.

The incidence of suspicious or positive smears in these 2,407 women was 1 per 89.

Those verified by histological examination were 1 per 120 patients. Unsuspected malignancy was found in 11 of 2,407 patients or 1 in 219.

DR. BAYARD CARTER, Durham, N. C.—Dr. Ferguson and Dr. Cavanagh in this detailed progress report have delineated the assistance which can be given by a registry of exfoliative oncology in the screening of patients, in the diagnosis, management, and treatment of cancer in a teaching hospital service. It is good to hear that each patient has cytologic studies. It is also good to know that when those patients who are eligible for the Registry leave the care of the clinic their clinical records and cytology reports are sent to the physician or to the clinic which will assume the follow-up care.

It is gratifying to us to hear that cytology screening is also done on all obstetric patients. Thirty-four of 443 patients were pregnant when tumor cells were first noted in



their smears. This is an essential feature of any cytology screening program. It is educational for the cytologists and in time probably will give some acceptable evidence as to the origin, or possible origin, of cervical cancer.

The results presented show that 130 patients had invasive cancers, that 59 patients had intraepithelial or Stage 0 cancers of the cervix and that 35 patients had basal-cell hyperplasia. These findings alone would justify the existence of an exfoliative tumor cell registry.

It might be noted here that the Inter-Society Cytology Council is considering a national registry to deal primarily with the cytologic and histologic aspects of intraepithelial carcinoma.

There is one technical question we would raise. Is it justifiable to use Papanicolaou's Class III nuclei as a basis for this Registry? It is a category for doubtful nuclei. In our laboratory, Class III includes not only the nucleus of doubtful status but the degrees of anaplasia which we consider to be related to intraepithelial cancer. The term "atypicalities" is applied to some of the nuclear changes classified in our Class III. Our opinion is that these patients certainly warrant careful clinical and cytologic follow-up. We do not believe, however, that they should be listed as patients with "positive" cytology. First, it has been our custom to avoid the use of the word "positive." As indicated by the essayists, it is an indefinite term. Second, we are among those, also indicated by the essayists, who believe that cells described as "positive" should be included only in Classes IV and V.

We ourselves have a registry comparable to the one described. All clinical examiners in our department have a part in the follow-up. We do not depend upon a social service alone. Our detailed classification of abnormal cervical cytology initiates follow-up studies in those patients who have Class IIA cytology or more severe changes. Therefore in our registry, which is maintained by our exfoliative cytology laboratory, it is not necessary for patients to have frank or suspicious tumor cells in smears to be followed. We feel it is essential in the study by exfoliative cytology of cervical carcinogenesis that the patients be followed who have definite but mild cervical atypicalities. We understand that our classification continues to be adopted for the segregation of degrees of cervical atypia.

The large percentage of false-positive error is difficult to explain. Figures are not shown to give the distribution of the 443 patients in Classes III, IV, and V. A large number in Class III would help to explain in part this error. Inadequate biopsy material or inadequate study of the biopsy material obtained also might explain in part this error.

We respect the section, "Patients With a Regression From Positive to Negative Cytology (Spontaneous Disappearance)." The essayists state very well the lack of understanding of this group of 118 patients. This is the group which in follow-up will give much valuable information on the alterations of the cytologic findings. The reporting of their procedures done on this group of patients is an experience common to all clinical efforts to discover the cancer site. We also are pleased with the statement, "The indications for conization in pregnancy have been the same as in nonpregnant women." It is also gratifying to know in the 13 pregnant women on whom conizations were done no abortions occurred. This parallels our experience but we have not had premature labor after conization.

From our survey of 69,300 patients from whom 292,300 smears have been studied we have approximately 410 patients with histologic Stage 0 cancer of the cervix. The rate of occurrence of this lesion in pregnant and in nonpregnant patients in our series is practically identical. We feel that the lesion of intraepithelial cancer is the same lesion in the pregnant woman as in the nonpregnant woman. We also feel that the lesion does not regress. We still believe that women under 30 years of age should be screened by cytologic techniques and we are glad to find that the essayists also approve the screening of all patients of any age.



DR. FERGUSON (Closing).—Dr. Carter has raised the question as to whether it is justifiable to use Class III in the designation "positive cytology." I believe the Registry will be more useful to the patients and will help us to understand better the place of cytology in gynecology and obstetrics if we include the Papanicolaou Class III slides. I do not believe it would be safe to exclude Class III. This can be explained best by reference to my Table VII. In this table you will see that 27 per cent of my patients with basal-cell hyperplasia had a Class III slide and 33 per cent of my intraepithelial carcinoma of the cervix patients had a Class III slide. Most important of all, 16 per cent of our cases of invasive carcinoma of the cervix had this least alarming of the three classes of smears. As long as these important diagnoses are going to provide smears that will be classified as only Class III, I believe that I will have to continue to include Class III slides in the Positive Cytology Registry. The degree of positiveness of the slide appears to be a very poor index of the speed with which a decisive diagnosis should be sought.

Dr. Johnson has suggested that my cases of spontaneous regression should be considered false positives. Undoubtedly some of the cases in the spontaneous regression ("spontaneous disappearance") group are false positives. Every large series of cases studied by cytology contains false positives. Again I want to emphasize that we have so many cases in this spontaneous regression group principally, I believe, because the Positive Cytology Registry follows these cases so effectively. This is the type of case that in many institutions is lost sight of and not studied further. It is quite natural when someone has a positive cytologic examination and all of the diagnostic studies yield no evidence of invasion that everyone breathes a sigh of relief and turns to patients who apparently need more of our attention. I should say that many of these cases of positive cytology in which cancer cannot be found are reviewed by our cytologists. The cytologists say, "These are cancer cells" or "These cells are so similar to and so suspicious of being cancer cells that I will have to continue to consider it a Class III slide." If on reviewing the slides the cytologist cannot make a statement like that, the patient is discarded from the Positive Cytology Registry.

## REGIONAL ANESTHESIA IN OBSTETRICS\*

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OVER the past twelve years, there have appeared numerous reports on the successful employment of regional anesthesia in obstetrics. Since 1946, more than 200,000 cases have been reported in the literature.

Hingson,<sup>1</sup> basing his opinion on reports from medical directors of drug companies which supply ampules for saddle block and caudal anesthesia, states that in 1947 more than one million ampules were prepared for saddle block anesthesia and more than 300,000 ampules for caudal administration. He further states that probably one half of the babies born in this country are delivered under regional anesthesia. There must be some reason for this trend.

Some medical centers, however, are reluctant to accept regional anesthesia for use in obstetrics because of possible untoward, severe, or even fatal results to the patient. We believe that such results as reported arise from errors in technique or judgment. This fact emphasizes the need for professional anesthetists and a rigid standard technique for the administration of this type of anesthesia in obstetrics.

Hellman<sup>17</sup> and others state that the use of oxygen prophylactically during labor and delivery and the use of expeditiously and properly timed intravenous fluids are just as essential to maternal and infant welfare as anesthesia and operative facilities themselves. These supporting measures, as well as participation in the sympathetic and reassuring approach, are the responsibility of the anesthesia staff.

With this in mind, in 1947 an arrangement was made with a group of professional anesthetists whereby the obstetrical service in St. Vincent's Hospital in Los Angeles would have a 24 hour coverage, thus making it possible for each patient to have a competent anesthetist in attendance for labor and delivery. We realize that we are more fortunate than most hospitals to have this service available; but it was felt that only full-time qualified anesthetists could eliminate complications that might result from regional anesthesia or indeed any other type of anesthesia used for delivery.

### Material

The cases reviewed in this paper cover a period from 1947 to 1957, inclusive. There were a total of 14,584 cases in which regional anesthetics were

\*Presented at the Sixty-ninth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 4-6, 1958.

used, as shown in Table I. There was an increase of regional anesthetics from 40 per cent in 1947 to 96 per cent in 1957. Also, it is interesting that since 1953 saddle block anesthesia has been diminishing and more caudal anesthetics have been given. This change is attributed to the fact that the anesthetists have acquired more experience in the giving of caudal anesthesia. Inasmuch as it eliminates postspinal headaches, a number of the attending obstetricians prefer it for their patients. These were all private patients in the middle-class income bracket and were delivered with few exceptions by men who are members of the American Board of Obstetrics and Gynecology or who are eligible to the Board. All of these patients were followed for a minimum of 6 months and over half of them for a period of 5 years.

TABLE I. FREQUENCY OF USE OF REGIONAL ANESTHESIA, 1947-1957

YEAR	TOTAL NO. OF DELIVERIES	TOTAL NO. OF SPINAL ANESTHETICS	TOTAL NO. OF CAUDAL ANESTHETICS	% OF REGIONAL ANESTHETICS
1947	1,990	788	1	40
1948	1,874	852	2	46
1949	1,777	823	3	47
1950	1,853	841	2	46
1951	1,868	1,110	32	61
1952	1,989	942	80	51
1953	1,967	1,368	363	88
1954	2,048	1,198	617	89
1955	1,926	854	819	87
1956	2,046	866	1,061	94
1957	2,048	782	1,180	96
Total	21,386	10,424	4,160	

### Technique

The patient is kept under moderate analgesia during the first stage of labor. When she is ready for delivery (for primigravidas, when the cervix is completely dilated and the presenting part is on the perineum; for multiparas, when the cervix is completely dilated), she is placed on the delivery table. The blood pressure is taken and recorded. The patient is then turned to the left lateral position in hyperflexion. The skin is carefully prepared with tincture of Zephiran and the patient is draped.

If a terminal caudal anesthetic is to be given, the sacral cornua are palpated. Local infiltration of the skin and deeper tissues is carried out with a 1 per cent solution of Xylocaine hydrochloride. With a No. 19 caudal needle, the sacrococcygeal ligament is pierced and the sacral hiatus is entered. Proper location of the needle in the caudal canal is tested by 10 c.c. of air in a shock wave and by the injection of a small test dose of Xylocaine hydrochloride. After a few minutes, when the anesthetist is assured that the needle lies in the caudal canal (epidural space), he injects 35 c.c. of 1 per cent Xylocaine hydrochloride with a few minims of 1:1,000 epinephrine.

If a terminal saddle block is to be administered, the third lumbar interspace is located. Local infiltration of the skin and deeper tissues is carried out with a 1 per cent solution of Novocain. Spinal puncture is made with a short-beveled 24 gauge needle, 3 inches in length. When a bead of clear spinal fluid is obtained, 40 mg. of a 10 per cent solution of Novocain is injected from a 2 c.c. syringe. The injection is made rapidly between uterine contractions in order to minimize erratic diffusion of the agent due to turbulence of the spinal fluid coincident with contractions.

The patient is quickly turned on her back, placed in the lithotomy position with the head elevated 30 degrees for 10 minutes. Six liters per minute of oxygen is routinely administered via plastic Boothby-Lovelace and Babouillian mask to minimize placental anoxia which might result following blood pressure changes.

Obliteration of perineal pain followed by uterine pain begins almost immediately with both forms of anesthesia. The anesthetic level attained with these techniques lies between the umbilicus and the xiphoid. Uterine contractions progress as before, for there is no obliteration of the uterine motor activity.

### Contraindications

Regional anesthesia is contraindicated in patients with previous spinal injury, neurological disease, chronic backaches, chronic headaches, local skin lesions precluding asepsis, in patients in whom a large loss of blood might be anticipated such as in placenta previa, in patients with marked hypotension, and in those who do not want this type of anesthesia. It is our belief that these contraindications should be adhered to rigidly.

### Complications

In spite of the great surge toward regional anesthesia, there have appeared in both the obstetrical and the neurological literature unfavorable or late neurological complications following this type of anesthesia. Our enthusiasm must then be tempered if acute and late sequelae develop in numbers. There were no maternal deaths as a result of these 14,584 regional anesthetics. No serious neurological sequelae or complications were encountered. No infections around the site of the injection were noted. There were a few cases in which temporary paresthesia developed in the lower extremities but these all cleared up without treatment.

The only untoward effects were hypertension and postspinal headache. The average drop in blood pressure was 10 mm. Hg systolic and 5 mm. Hg diastolic. No instances of spinal shock and collapse were observed.

True postspinal cephalgia occurred in 8 to 12 per cent of the patients. In the past 2 years, however, since the introduction of smaller caliber spinal needles, the incidence of headaches is now about 4 per cent. These headaches usually come from 24 to 48 hours after delivery and as a rule subside in 3 to 6 days. Rarely were patients forced to remain in the hospital because of this complication. Like all other users of regional anesthesia, we have tried numerous medications to alleviate postspinal headaches. No one type of medication has proved successful in our hands.

### Advantages of Regional Anesthesia

Since we have never liked local anesthesia in obstetrics, in our opinion the only competition to regional anesthesia is given by inhalation. The advantages of regional anesthesia are that the patient for the most part is conscious and can feel that she is taking part in her delivery. She frequently hears the baby's first cry and sees her child immediately. This gives a tremendous psychological boost to most mothers. We have found that fetal depression and anoxia are rare as compared to these effects with inhalation anesthesia. The risk of inhalation of vomitus has been eliminated almost entirely and with it the complication of aspiration pneumonia. Merrill and Hingson<sup>2</sup> estimated that there are at least 100 deaths per year in this country from aspiration of vomitus following inhalation anesthesia.



With increased pelvic floor relaxation as obtained with regional anesthesia, we feel that the operative procedure of manual rotation or forceps rotation has been much less difficult. With increased contractility of the uterine musculature, shortening of the third stage has been apparent, with a resultant decrease in total blood loss of the mother. There is no hurry in the delivery and there is ample time for repair without subjecting the mother to prolonged inhalation anesthesia and its risks.

### Comment

It is our belief that regional anesthesia is the anesthesia of choice in obstetrics when given by a professional anesthetist. Seegar and Devlin<sup>3</sup> reported on 5,250 patients who had saddle block anesthesia at St. Agnes Hospital in Baltimore. They concluded that paralysis from saddle block anesthesia is rare and that until better obstetrical anesthesia is offered, it is far safer than inhalation and more satisfactory than local anesthesia. Macer<sup>4</sup> reported 34,936 cases in which regional anesthesia was used for delivery in two private hospitals in our adjacent city of Pasadena. In this large series, there were no maternal deaths from anesthesia and no neurological complications of any consequence. These anesthetics were given by the attending obstetrician, an arrangement of which, however, we do not approve. Sadore and Levin<sup>5</sup> reported 10,000 cases of delivery by regional anesthesia without any permanent paralysis. Reed,<sup>6</sup> in reporting 174 cases of cesarean section done under regional anesthesia, stated, "There have been no neurological complications." Makepeace,<sup>7</sup> in reporting on 1,840 regional anesthetics for delivery, concluded that no known damage due to the anesthetic was found. One patient had meningismus probably due to hemorrhage from the spinal puncture. Dripps and Vandam<sup>8</sup> in 1954 reported upon 10,098 patients given regional anesthesia on their surgical service at the University of Pennsylvania Hospital. In this large series, there were no instances of permanent neurological disease. A few immediate complications disappeared within 2 weeks, the longest lasting 6 months. De Carle,<sup>9</sup> in a review of regional anesthetics for cesarean sections, noted that there were less morbidity and mortality for both mother and child with regional anesthesia than with inhalation anesthesia. No serious neurological complications occurred in his large series.

On the other hand, Greenhill<sup>18</sup> stated that spinal anesthesia is the most dangerous type of anesthesia for the pregnant woman. Nicholson and Eversole<sup>10</sup> found 5 patients with major neurological sequelae in 21,000 cases in which regional anesthetics were given for general surgical procedures. Bergner and associates<sup>11</sup> in 1951, from the University of Tennessee, reported 6 cases of paralysis following regional anesthesia. Rosenbaum and co-workers,<sup>12</sup> from St. Louis, in 1952 reported six cases of adhesive arachnoiditis in 1,772 patients who had been given saddle block anesthesia. Holder and Graves,<sup>13</sup> in a review of 32,822 regional anesthetics for both obstetrics and general surgery, reported 16 neurological complications. However, only 4 of the 16 could be classified as severe or as showing persistent symptoms, an incidence of one severe complication in 10,000 anesthetics. They suggest that meticulous technique and abandonment of continuous spinal anesthesia can further reduce the incidence of these complications. They were also of the opinion that some of these patients with complications following regional anesthesia might possibly have had pre-existing neurological disease which should have been a contraindication to the use of this type of anesthesia. Thorsen<sup>14</sup> of Sweden reported on a series of 2,493 cases in which regional anesthetics were administered, with an incidence of neurological complications five times as great as that reported by Holder and Graves. However, the accuracy of Thorsen's conclusions is open to question since the data he reported were obtained by

questionnaires sent to the patients. Kennedy, Effron, and Perry<sup>15</sup> reported 12 cases of grave paralysis admitted to Bellevue Hospital following regional anesthesia. Whether or not this type of anesthesia should have been used in all these cases is certainly another question. Dodge<sup>16</sup> of the University of Arkansas reviewed the records of 3,147 patients who had received regional anesthesia. She was able to get 1,077 patients back for examination. Less than 1 per cent showed neurological changes which might be related to saddle block anesthesia and probably only 0.5 per cent were related to the anesthesia. She concluded that this is an unusually low rate for late anesthesia complications of any kind, and her clinical experience does not indicate this method to be a hazardous form of anesthesia.

### Summary

1. A total of 14,584 obstetrical patients were given regional anesthesia.
2. There were no maternal deaths due to anesthesia.
3. There were no serious neurological complications or sequelae in this series.

### Conclusion

While at first glance this study and analysis may seem like a repetition of many similar papers that have appeared in the literature, yet this is the first time that this subject has been laid before the Association.

The senior author of this paper (B. J. H.) has taken this opportunity to separate once and for all the wheat from the chaff that has so clouded the subject. I feel that it is time for the obstetricians of this country to take a long, clear, hard look without bias at the use of regional anesthesia in obstetrics. I have used this modality since 1930 and during this time have yet to observe a fatality or permanent disability arising from it. Others can support this observation.

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### Discussion

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—Presentation of results so unimpeachably good as those of Drs. Hanley and McNulty makes discussion somewhat difficult. With

no maternal deaths and only a few instances of transient nerve damage in so large a number of deliveries there can be little surprise at the ever-increasing percentage of patients delivered under regional anesthesia.

Such an enviable record attests the high-caliber staff of professional anesthesiologists and more especially to the 24 hour coverage so necessary and yet so infrequently available to obstetric services in this country. The record also bespeaks the meticulous care taken to avoid and guard against those rare but omnipresent accidents which can accompany regional anesthesia. Perhaps the shift to terminal rather than continuous caudal constitutes one of these precautions.

With but 4 per cent of patients being delivered by other than regional anesthesia, one must assume that the authors recognize but few obstetrical contraindications to its use. Granted most of the placenta previas will be delivered by cesarean section; what of the abruptio placentae, of the cases of breech and of acute toxemia? In my own experience with breech and caudal, I have found this combination feasible but not too desirable. In acute toxemia the lability of the blood pressure constitutes a hazard under any anesthetic and more particularly under spinal and caudal block.

These are but minor considerations. From the record it is altogether evident that breech, toxemia, etc., notwithstanding, these fine results could have been achieved only by a combination of a high order of anesthetic and obstetric skill.

The point I really wish to discuss is Dr. Hanley's conclusion that this paper has separated the wheat from the chaff. I feel it has done somewhat less than this. The paper says only that under certain restricted conditions of environment, personnel, and patient, safe results for the mother could be obtained with terminal regional anesthesia in a very high percentage of all deliveries. There is really no mention of degree of patient satisfaction or dissatisfaction although it is well known that always and everywhere, even with Hingson, the master, some caudals must fail. Nor, surprisingly, is there any mention of safety for the baby.

Each proponent of a method of pain relief for delivery has claimed its superiority in maternal and infant safety and maternal satisfaction—and he has proved this beyond a shadow with statistics. As in Carl Sandburg's snatch of song about all cigarettes being milder than all other cigarettes, so it is with childbirth anesthesia and so it has been since that day in November, 1847. Statistics by the ream to the contrary, none of these claims is provable from a scientific and controlled viewpoint. Human experience in this regard has too many variables and has never yet been available to controlled experimentation. Nor can sound conclusions be drawn from a common-sense viewpoint. For example, one would suppose that by far the safest maternal situation would exist with no anesthesia at all, as in a 96 per cent Grantly Read maternity, while perhaps by far the greatest patient satisfaction and infant safety might be derived from a 96 per cent continuous caudal pavilion. Neither is entirely correct. In the first instance the anesthesiologist and his machines would have so far decayed that in an emergency situation requiring his best skill and judgment he could offer neither, while, in the latter case, satisfactory as is good caudal, and there is none better when it works, it is as bad as bad can be when it fails. Unfortunately this is about 4 or 5 per cent of the time. Further, the question is now being seriously raised by Kohl and Kaltreider and others as to whether this type of nontransplacental anesthesia is really safest for the jeopardized infant.

Time and time again it has been demonstrated that given specific conditions almost any method of pain relief will give astoundingly good results. As the skill and experience of the staff increase, these methods can become unbelievably complicated and still retain a margin of safety, but such techniques cannot be transplanted with the same safety to different environments. In my own situation the transplantation of the rather complex techniques that Dr. Hingson and I employed in a refined atmosphere at the Hopkins would have been disastrous in a large municipal hospital in Brooklyn. Such a hospital requires a simple technique with a distribution of anesthesia similar to that shown



in Table I. I venture to suggest that Dr. Hanley finds this true in his other hospital also. We find a local block with cyclopropane supplementation with the Reserve Midget when necessary quite our best and safest bet.

TABLE I. ANESTHESIA FOR VAGINAL DELIVERIES AT THE STATE UNIVERSITY OF NEW YORK, 1954-1956  
(OVER 1,000 GRAMS BIRTH WEIGHT)

ANESTHESIA	NO.	%
None	5,974	43.2
Encephalic	432	3.1
Saddle block	930	6.7
Caudal and/or epidural	117	0.8
Local	5,683	41.1
Conduction + encephalic	699	5.1
Total	13,835	100.0

Perhaps in our present state of knowledge the best that can be said about "wheat and chaff" is that whereas all methods work admirably most of the time, the wisest course is to aim for the simplest anesthetic technique compatible with the intellectual mores of the patient but never to employ one whose complexities exceed the capabilities of the staff.

DR. R. GORDON DOUGLAS, New York, N. Y. (for DR. H. HUDNALL WARE, Richmond, Va.).—Drs. Hanley and McNulty have reported their experiences with obstetrical anesthesia during an 11 year period. Their decision in 1947 to provide all of their patients with the services of a trained anesthesiologist represents foresight and sound judgment that has paid handsome dividends in the provision of safe anesthesia to their private patients since that time. No maternal deaths and no serious neurological complications are recorded. Unfortunately no reference is made to fetal results nor indeed the degree of anesthesia obtained.

In the first 4 years of the study caudal anesthesia was employed only 8 times, while during the year 1957 this technique was used in 1,180 cases. Spinal anesthesia was employed with some increasing frequency during the middle years of the study but with approximately the same frequency during the first and last year of the study period. These changing trends suggest increased interest and familiarity on the part of the anesthesiologists with the caudal technique. I presume there was a comparable decrease in the employment of inhalation anesthesia during the same time. The technical ability of the anesthesiologists is attested by the fact that spinal or caudal was employed in 96 per cent of their patients during the year 1957. The fact that terminal anesthesia was not given until the cervix was fully dilated, and, in the case of the nulliparous patient, while the head was on the perineum, is of significance and an achievement that could not be obtained in the New York Lying-In Hospital.

Many reports in recent years have left no doubt that anesthesia is responsible for a significant proportion of maternal deaths in this country. Untrained personnel and faulty techniques have been largely responsible. Trained anesthesiologists to administer or supervise all anesthesia is, I believe, a major need. This will necessitate continually expanding resident training programs in this discipline. This means, of course, that in teaching hospitals with such programs residents will administer anesthesia under supervision.

It is quite conceivable to me that in another hospital, comparable in size to St. Vincent's, a group of equally qualified anesthesiologists could achieve equally good results employing inhalation anesthesia in 96 per cent of cases. I do not believe, however, that either system represents the ideal. The armamentarium of the anesthesiologist should provide anesthesia to meet the needs of the individual patient. A few patients neither need nor will accept anesthesia. In some others, local infiltration supplemented



with inhalation analgesia for a brief period is all that is required. I believe that pudendal block is also a valuable part of our armamentarium—that it is safe and suitable for a relatively large group of patients. In other instances, general inhalation techniques will provide the best results. Certainly spinal and/or caudal provides a valuable method as a part of such a general program.

In the New York Lying-In Hospital during the past decade, increasing attention has been directed to the educational needs of the patient and her need of emotional support during pregnancy, labor, and the puerperium. The program includes group instruction courses during pregnancy and increased emotional support during labor. Physical support is not neglected. It has been interesting to observe skepticism on the part of the attending and resident staff turn to enthusiasm. The program is in no way directed at withholding analgesia during labor, but considerably less analgesia has been used. During the same time the incidence of prolonged labor has decreased. When terminal analgesia is indicated, the patient is better nourished, better hydrated, more emotionally stabilized, and, as a result, is a better candidate for anesthesia of any type.

DR. HAROLD HENDERSON, Detroit, Mich.—I wish to report our experience with local anesthesia in obstetrics. We have used predominantly low spinal, but caudal and pudendal block have also been frequently employed.

In 1927, stimulated by the fact that many surgeons were using spinal anesthesia, we began to follow suit. In the next 6 to 7 years I personally used procaine block in about 750 cases. The results were very good. We had no deaths and no neurological complications. After that, since DeLee and later Greenhill condemned the method, we became a little cautious. We felt that it would be difficult to justify our procedure when such outstanding men were opposed to its use.

In the late thirties we began employing it again with a smaller dose and improved technique. We used Metycaine and Pontocaine as well as procaine. About that time Arthur Hunt reported the use of spinal anesthesia in 500 cases in obstetrics at the Central Association Meeting in Chicago. Similarly Cosgrove and Adriani braved the possibility of a malpractice suit and popularized this method. We continued to use it and now this method is used in at least 95 per cent of our cases.

About 10 years ago Bittrick and Rangetore from our hospital reported 1,000 cases of spinal anesthesia in obstetrics and were very enthusiastic about it. There were no deaths in this series but they reported the usual number of spinal headaches. Since that time we have an accumulated experience of about 40,000 cases. We had one death which we feel was due to failure to recognize a drop in blood pressure. There were 6 cases of meningitis. In all of these the cultures were negative and the patients made prompt recovery after spinal tap and the use of antibiotics. During this time we had 4 deaths from aspiration following the use of general anesthesia. In addition, bronchoscopy was done in several cases of aspiration in which the patient did not die.

Dr. Hanley has a perfect setup because the anesthetic is administered by trained men. Our setup is good but not so good as his. We have in our hospital two competent anesthesiologists and three residents in training, but they do not cover our service. However, our residents spend the first 3 months of their service under the tutelage of our chief anesthesiologist. They give most of the spinals and either they watch the patient or she is watched by our nurse anesthetist. Few hospitals can have as perfect coverage as described in the paper but many of them can provide a satisfactory service by additional training of their obstetrical residents.

DR. F. J. HOFMEISTER, Milwaukee, Wis.—The author has submitted a significant series of cases under regional anesthesia without a maternal catastrophe. These were done under conditions where the anesthetic program was well supervised. It is our experience that this is not always so in the smaller hospitals. In fact, some hospitals do not enjoy the luxury of an anesthetist. The Maternal Mortality Committee of Wisconsin is impressed with the seriousness of this matter.

I would be remiss if I did not quote some of the figures gathered from our experience and used as teaching material for general practitioners. In 5 years of our study, we have had 3 deaths from caudal anesthetics in the state of Wisconsin, we have had at least 2 deaths associated with inhalation anesthetics, we have had one death due to a spinal anesthetic. There have been several deaths directly associated with Trilene analgesia followed by Trilene anesthesia. These figures indicate the fact that hazards exist in the majority of institutions where obstetrics is practiced and there is no specialized anesthetic service.

DR. HENRY L. DARNER, Washington, D. C.—In our Blue Shield planning we are having an increasingly difficult economic problem in the case of the obstetrician who is using this modality himself for obstetrics and sending us a full bilateral fee. I hope that Dr. Hanley in the conclusion to his paper will permit me to carry back to my Board a word of encouragement that he stressed the fact that he considers this a non-hazardous procedure when he has a diplomate of the Board of Anesthesiology give his anesthesia but a hazardous procedure if this modality becomes generally used by the obstetrician in the smaller hospitals.

DR. J. ROBERT WILLSON, Philadelphia, Pa.—We have had a considerable amount of experience with regional anesthesia, having given somewhere between 15,000 and 20,000 such anesthetics since Dr. T. L. Montgomery introduced spinal anesthesia at Temple University Hospital in about 1940. It seems to me, however, that when 96 or 98 per cent of patients are delivered with spinal anesthesia, it is like shooting flies with a 12-gauge shotgun.

The obstetrician should analyze his own aims and needs in anesthesia and not consider that he is giving it only for the benefit of the patient. It seems completely illogical to me to give either caudal or saddle block anesthesia to a multipara who is going to be delivered with a few more contractions. In many instances I suspect that the patient is even prevented from delivery by the sitting position required to administer the saddle block anesthesia. I suggest that instead of talking about complete relief of pain, satisfied patients, and so on, we consider why we select a regional anesthetic for a patient. Is it actually important for her or is it only to keep her still, making the delivery a bit easier for the obstetrician even though it does increase the risk?

DR. HANLEY (Closing).—Dr. Willson brought up the question of not giving anesthesia to multiparas. These were all private patients who had come to their physicians for adequate care. In my opinion this means relief of pain to the extent that can be done with safety to both the mother and the child.

Dr. Gordon Douglas stated that any type of anesthesia will give good results in about 96 per cent of selected cases. With that I agree. I used inhalation anesthesia for a number of years. However, the same anesthesia that puts the mother to sleep puts the child to sleep. If spontaneous respiration did not occur in the baby immediately following delivery, then, of course, one was faced with resuscitation.

I have used spinal anesthesia in obstetrics for the past twelve years and in all gynecological procedures since 1930. I think it is the best anesthesia we have at the present time. When a better one is developed, I shall gladly change.

## THE REPAIR OF URETERAL INJURIES\*

### Experimental Studies, Clinical Application, and Review of the Literature

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URETERAL injuries are increasing in frequency. The decline in obstetric injuries, so prevalent a half century ago, has been replaced by an increase in surgical or radiologic injuries. Despite this increase, a review of the papers presented before this Association over the past decade reveals only two on this subject.<sup>1, 2</sup>

A study of our own experience has suggested there are three types of ureteral injury on the basis of etiology. First are surgical accidents, occurring as a consequence of distorted anatomy or difficult surgery. Second are the ureteral injuries which are deliberate, the intentional severing or resection of part of the ureter during the course of surgical dissection. These injuries obtain almost entirely in the primary or palliative management of pelvic malignancies. And, third, there are the injuries which we choose to call secondary or ischemic, those which result from the combined effects of surgery, radiation, and/or infection on the blood supply of the ureter and surrounding tissues with the consequent necrosis.

The true incidence of each of these is unknown since in many patients the ureteral obstruction is complete and the patient convalesces without symptoms. In a state such as Arkansas, however, with only one charity clinic, it appears unlikely that symptomatic ureteral injuries have escaped our detection since these patients uniformly return here for medical care. During the past 10 years, it is estimated that there have probably been 10 accidental ureteral injuries in the Department; 6 have been identified and repaired either at the time of operation or subsequently. In addition, there have been 73 deliberate ureteral injuries performed during the course of exenteration operations for radiation-resistant carcinoma, or as palliation for ureteral obstruction.

Our management of these problems has followed traditional patterns, ureteroureteral anastomosis, ureterocystostomy, various ureteral substitution and grafting procedures, urinary diversion through ureterosigmoidostomy, and an occasional temporary cutaneous ureterostomy. In a few instances, a surgical or autonephrectomy has solved the clinical problem.

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A review of our early experience disclosed some unsatisfactory results classified variously from fair to poor. An analysis of these unsatisfactory results suggested that, although there were many variants which affected the clinical course of events, there appeared to be two fundamental problems that were primarily responsible. The first of these was stricture formation at the site of anastomosis, resulting in hydronephrosis with its attendant infection and ultimate renal destruction. The second major problem, fortunately less common, was urinary leakage, either as incontinence (fistulas) or extravasation. To shed some light on these major causes of failure, a series of experiments<sup>3</sup> was designed to explore the factors influencing stricture and leakage.

### Experimental Studies

*General.*—Adult mongrel dogs were used for these studies. They were cared for in the animal surgical division of the University of Arkansas Medical Center. Anesthesia was predominantly intraperitoneal Nembutal. All dogs received procaine penicillin, 300,000 units daily, for 5 days postoperatively. All splint catheters were of polyethylene plastic and varied from size PE50 to PE190. (External diameter .038 to .067 inches; F. 2.9 to 5.1.)

In the ureterosigmoidostomy experiment, the bowel was prepared by castor oil and Sulfasuxidine.

The animals were sacrificed at intervals from 10 to 150 days and the entire urinary tract dissected out for study. All anastomoses were done by the Cordonnier mucosa-to-mucosa technique, with No. 4-0 or 5-0 chromic catgut on Atraumatic needles.

*Cortisone.*—Baker and associates<sup>4, 5</sup> had suggested that cortisone might reduce the fibroblastic proliferation about an anastomosis and thereby reduce stricture formation. To explore this possibility, a group of 8 dogs weighing between 15 and 25 pounds were prepared as indicated above and bilateral ureterosigmoidostomy was done, the ureters being placed as low in the bowel as possible.

Postoperatively, in addition to routine care, these dogs received 25 mg. cortisone acetate intramuscularly daily for varying periods of time, and an autopsy was performed in 30 to 144 days (Table I). Two dogs (Nos. 21 and 22) served as controls and were managed in the same way except they did not receive cortisone.

*Intubation.*—Sutures and suturing techniques have been held responsible for much of the scar tissue and stricture formation. To eliminate these possible effects, a series of 4 dogs was prepared and the ureter transected in its lower one third. Snug but not tightly fitting polyethylene catheters were threaded into the renal pelvis and into the bladder. No sutures were employed. The cut ends of the ureter were loosely approximated and held by the adventitia. The postoperative care was as described above, and the catheters were removed at intervals of from 10 to 19 days. The animals were subjected to autopsy in from 10 to 38 days (Fig. 1).

*Regeneration.*—A third set of experiments was conducted in which 1 inch was resected from the lower one third of the ureter. A polyethylene catheter was placed to bridge the gap and the ends of the ureter were held apart by anchoring silk sutures placed through the adventitia of the ureter and the underlying fascia. These sutures also served as identifying marks for subsequent study. The animals received the routine postoperative care indicated above. The catheters were removed (or came out inadvertently) in from 6 to 27 days and autopsies were performed at from 7 to 39 days (Fig. 2).



**Tube Graft.**—The final series of experiments utilized a pedicle tube graft of bladder wall. In 2 dogs the tube was closed over a polyethylene catheter to the end of which the severed ureter was anastomosed by the Cordonnier<sup>6</sup> technique. The catheter extended from the renal pelvis to the bladder and the end was secured in the vagina. The catheters were removed in 21 and 30 days and the animals were autopsied on the twenty-fourth and fortieth days.

TABLE I. EFFECT OF CORTISONE ON HEALING OF URETEROSIGMOIDOSTOMY

D O G # STATUS	DAYS RX	DAYS P.O. AUTOPSY	URINARY OBSTRUCTION		RENAL INFECTION		D O G # STATUS	DAYS P.O.	DAYS OF RX	URINARY OBSTRUCTION		RENAL INFECTION	
			L.	R.	L.	R.				L.	R.	L.	R.
21 A	0	55	-	+	-	0	14 A	30	28	0	0	+++	+++
22 A	0	55	-	++	-	+	11 D-U	39	36	++	0	+++	+++
14 A	28	30	0	0	+++	+++	3 A	50	30	+	+++	+++	+
1 A	30	136	0	0	0	0	2 A	52	30	++	++	+++	+
2 A	30	52	++	++	+++	+	21 A	55	0	-	+	-	0
3 A	30	50	+	+++	+++	+	22 A	55	0	-	++	-	+
11 D-U	36	39	++	0	+++	+++	4 D-U	60	58	+++	++	?	?
*4 D-U	58	60	+++	++	?	?	*8 D	99	63	++	++	+++	+++
*8 D	63	99	++	++	+++	+++	1 A	136	30	0	0	0	0
17 A	104	144	+	+	+	+	17 A	144	104	+	+	+	+

A.  
DURATION OF CORTISONE TREATMENT

B.  
DURATION OF ANASTOMOSIS  
(DAYS P.O.)

NOTE: STATUS: A=ALIVE; D=DEAD; U=UREMIA.  
RX: TREATMENT - CORTISONE 25 MG. IM DAILY.  
\*: TISSUE LOST ON DOGS 4 & 8. BOTH HAD SEVERE PYELONEPHRITIS (GROSS).  
SYMBOLS: 0=NO EFFECT; -=NO RECORD; +=MILD; ++=MODERATE; +++=SEVERE.

Data arranged by increasing duration of cortisone treatment, A, and by duration of anastomosis, postoperatively, B; no correlation is noted. Dogs 21 and 22 are control animals.

## Results

The results of these experiments are indicated in Table I and Figs. 1 and 2 and amplified by the photographs (Figs. 3-10).

**Cortisone.**—In all of the 8 animals that received cortisone postoperatively, the ureterointestinal anastomosis had healed and was grossly patent and functioning. Of the 16 kidneys involved, however, 12, or 75 per cent, showed varying degrees of gross and/or microscopic evidence of infection, and 11, or 68 per cent, had hydroureter and hydronephrosis. Two dogs died of uremia and one dog had an abdominal wound infection. In 2 animals there was clinical and microscopic evidence of infection at the sites of 3 anastomoses. The 2 control animals had unilateral ureterosigmoidostomy. Both transplanted urinary tracts showed some hydroureter and hydronephrosis and in one animal there was mild infection (Table I).

The study of the sites of anastomoses failed to reveal any significant difference in the fibrous tissue formation in the cortisone-treated and the control animals<sup>7</sup> (Figs. 3-5).

**Intubation.**—The unsutured ureter had healed in all the dogs. At 10 days healing was incomplete, but by 14 days and longer both the muscular and epithelial layers had regenerated. Varying degrees of stricture were present and there appeared to be an inverse relationship between the length of time the catheter was in place and the degree of stricture. There was no extravasation or leakage of urine about the approximated but unsutured ends of the ureters (Figs. 1 and 5).

INTUBATION TECHNIC STUDY						
Dog	Postoperative Day Catheter Out	Postoperative Day Autopsied	Result	dist.	Illustration	prox.
K	10	10	Incomplete healing. No hydrourter			
F	11	38	Complete stricture. Dense scar. Severe hydrourter			
G	14	35	Mild stricture. Epithelium regenerated. No hydrourter			
M	19	23	Mild stricture. Epithelium regenerated Moderate hydrourter			

Results of transection of ureter and treatment with polyethylene catheter intubation technic. Catheters were removed or expelled at intervals of 10 to 19 days. Autopsies were performed at intervals of 10 to 38 days postoperative.

Fig. 1.

URETERAL REGENERATION STUDY						
Dog	Postoperative Day Catheter Out	Postoperative Day Autopsied	Result	dist.	Illustration	prox.
A	6	7	Acute inflammatory mass Severe hydrourter			
D	8	39	Complete stricture. Dense scar mass. Severe hydrourter			
B	11	32	Severe stricture. Epithelium regenerated. Severe hydrourter			
E	13	37	Moderate stricture. Epithelium incompletely regenerated. Mod- erate hydrourter.			
I	23	23	Mild stricture. Epithelium regenerated. Mild hydrourter (gross only)			
C	27	27	Mild stricture. Epithelium regenerated. Mild hydrourter			

Results of resection of one-inch segments of ureter. Ends of ureter threaded over polyethylene catheter. Catheters removed or expelled at intervals of six to 27 days. Dogs autopsied at intervals of seven to 39 days postoperative.

Fig. 2.

**Regeneration.**—In Dogs A and D (Fig. 2), the catheter was removed in less than 10 days and there was a mass of inflammatory reaction and complete ureteral obstruction at the site of resection. In the 4 remaining dogs, intubated for 11 plus days, there was epithelial and muscular regeneration of varying degree over the inch defect (Fig. 2). There was noted an inverse relationship between the duration of intubation and the degree of stricture. The gross and microscopic picture of the ureter at 28 days appeared normal (Figs. 6, 7, 8, 9, and 10).

**Tube Graft.**—The catheters were left in place in these 2 dogs for 21 plus days. At this time there was complete epithelial and muscular anastomosis. There were inflammatory changes about the sutures of the graft and some intermittent inflammatory masses. The ureter above the graft appeared normal and the kidneys were normal. There was no evident stricture although in some areas the caliber of the graft varied.

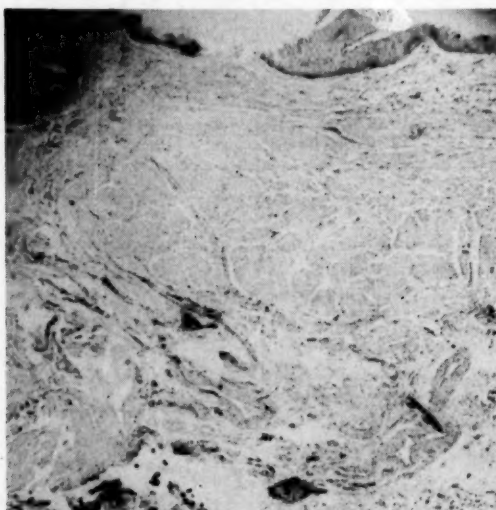


Fig. 3.

Fig. 3.—Dog, 1, Table I. Treated with cortisone for 30 days. Autopsied on one hundred thirty-sixth postoperative day. Section at site of ureterosigmoid anastomosis.

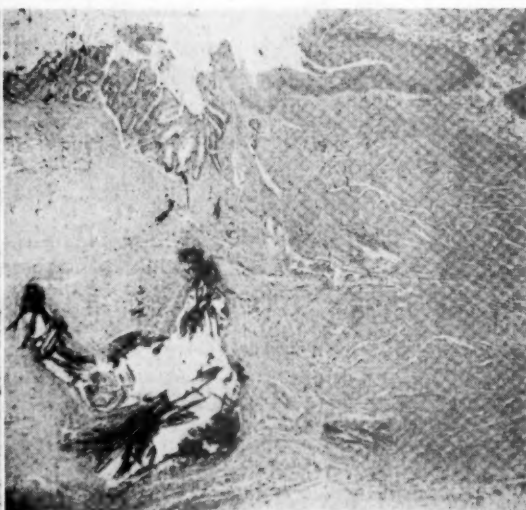


Fig. 4.

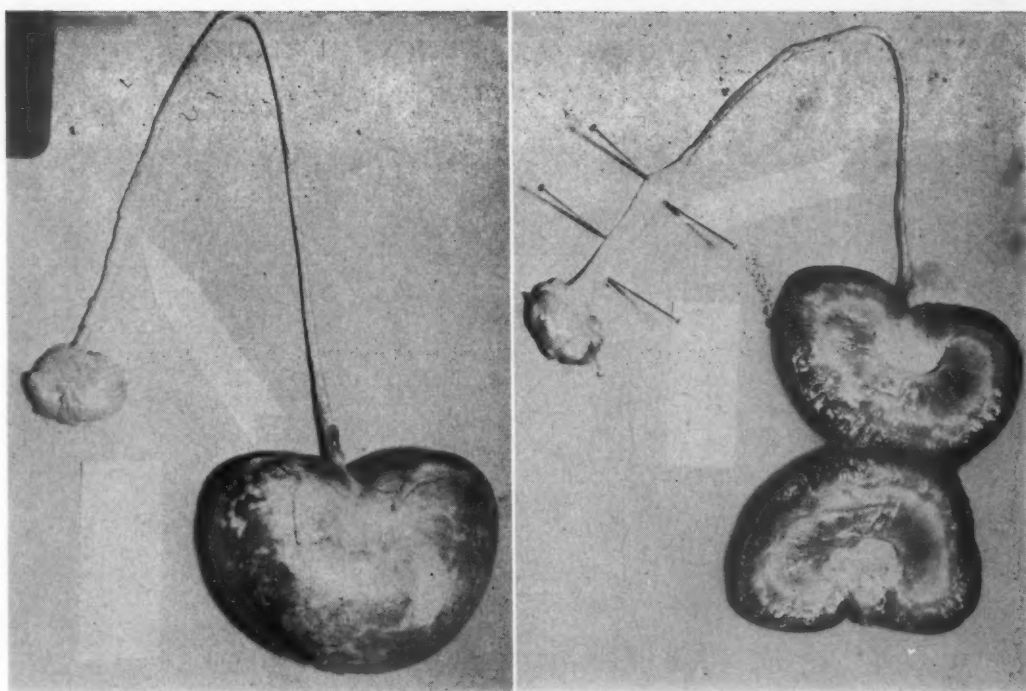
Fig. 4.—Dog 21, Fig. 1. Control dog. Autopsied on fifty-fifth postoperative day. Section at site of ureterointestinal anastomosis. No significant difference in fibroplasia as compared with Fig. 3.

**General Comments.**—The care of these animals proved difficult at times. Four of the 22 animals died of various causes. Some difficulties obtained in securing the catheters and finally it was determined that if female dogs were used the external end of the catheter could be sutured inside the vagina where it was accessible for removal but could not be removed by the dog. These factors account for the irregular schedules of some of the intubations and autopsies.

It seems appropriate to comment on the almost complete absence of reaction about the polyethylene tubing. The only inflammatory changes were in the tube graft. There was no detectable inflammatory reaction in the ureter, kidney, or bladder. No encrustations were noted on the outside and only minimal deposits were noted within the lumen of the catheter.

### Clinical Applications

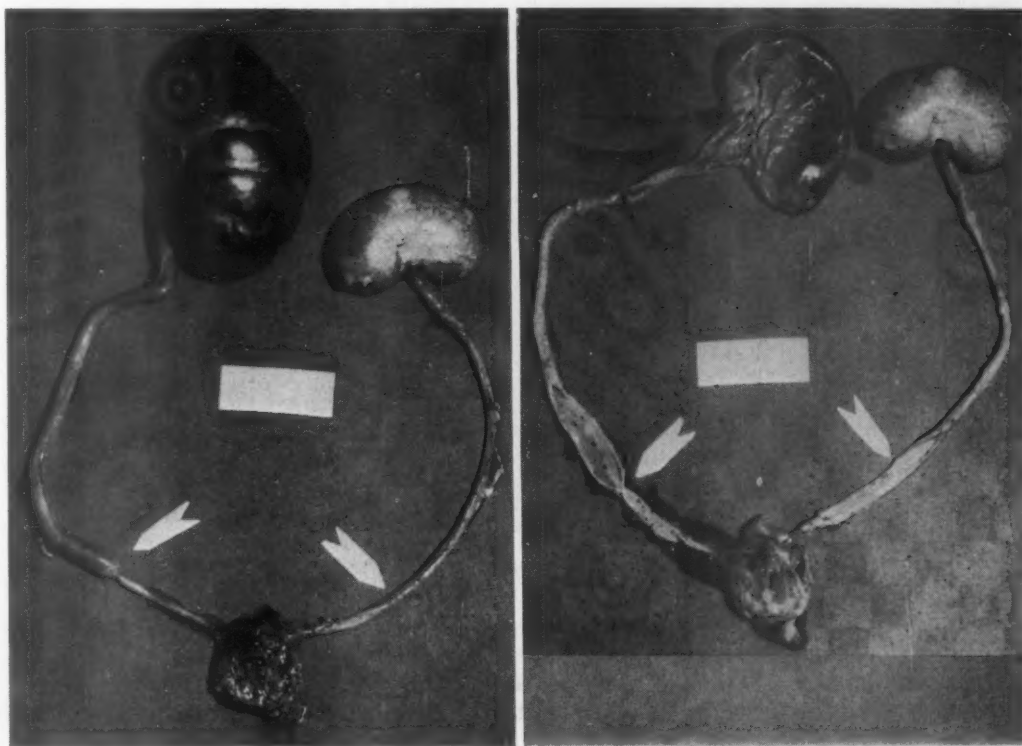
From these observations, certain clinically applicable conclusions seemed available. The first of these was that antibiotics, antifibrotics, and mucosa-to-



A.

B.

Fig. 5.—Urinary tract of transected left ureter of Dog M, Fig. 1. Tube indwelling 19 days. A, Closed. B, Open. (Note minimal scar and absence of hydronephrosis.)

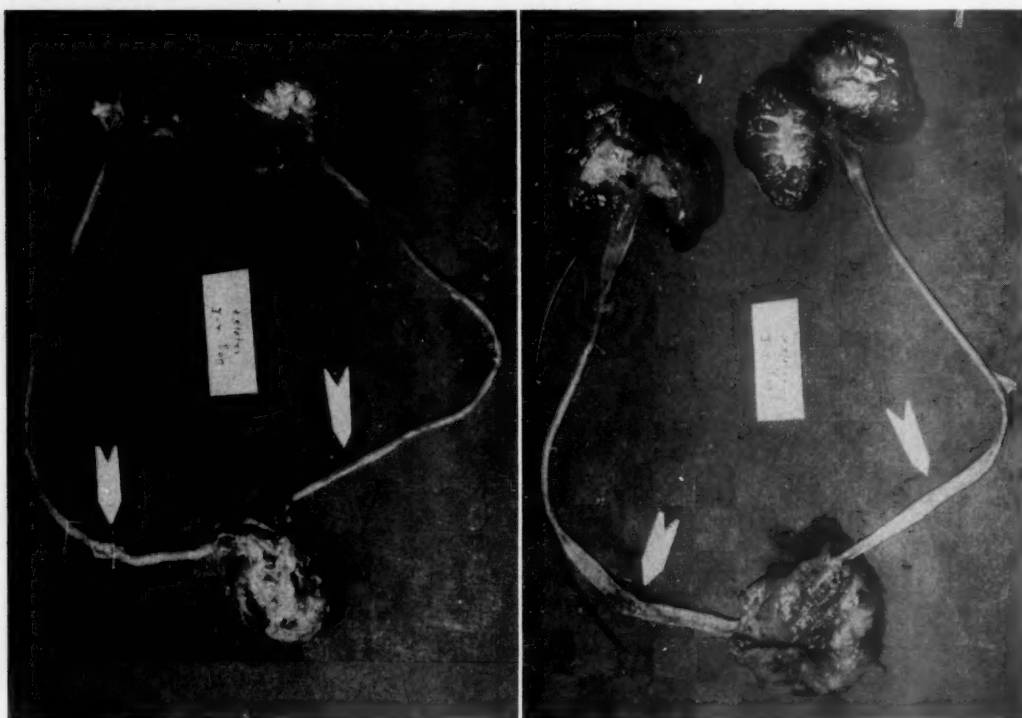


A.

B.

Fig. 6.—Urinary tract of resected ureter in Dog B, Fig. 2. Catheter came out on eleventh day. A, Closed. B, Open. (Note stricture and hydroureter and hydronephrosis.)





A.

B.

Fig. 7.—Urinary tract of dog with resected ureter intubated 27 days. Dog autopsied on twenty-seventh day. A, Closed. B, Open.

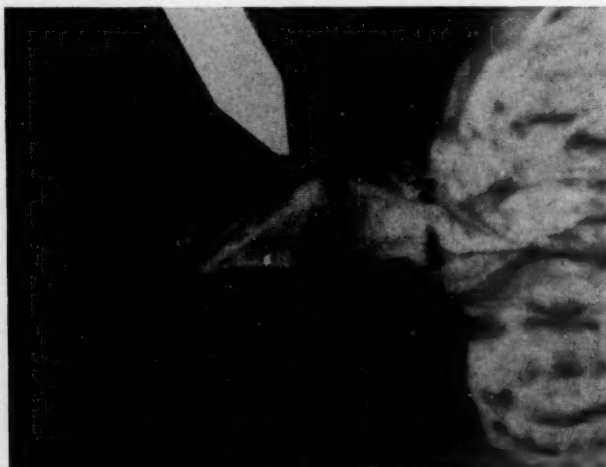


Fig. 8.—Photograph showing regeneration of ureter. Arrow points to opened ureter where 1 inch segment was removed 27 days previously. Opened bladder on the right. Dog C, Fig. 2. See Figs. 9 and 10.

mucosa anastomosis would not obviate the inflammatory tissue reaction to suture material or infection with subsequent stricture of the ureterosigmoidostomy. Second, a suture closure of the ureter was not necessary, from the standpoint of either healing or leakage and extravasation. And third, polyethylene is biologically essentially inert and that (within reason) the longer the catheter splint is left indwelling, the better the healing and the less stricture obtained.

When these observations were added to the established principles of plastic surgery, good blood supply, absence of foreign body, freedom from tension, immobilization, and asepsis, good clinical results should obtain.

Consequently, since 1953, ureteral injuries, either accidental, deliberate, or ischemic, have been handled by these principles. When possible, a ureterocystostomy is employed with split ureteral ends turned back inside the bladder and the anastomosis splinted with polyethylene catheter (Fig. 11). As an alternative, ureteroureteral anastomosis over a polyethylene tube with a minimum of No. 4-0 or 5-0 chromic sutures for loose approximation was employed.

If the tissue loss was such that additional length was required, the bladder tube graft was employed, with minimum suture and a polyethylene splint catheter. Experience has suggested that a small cystotomy wound with polyethylene coming through the abdominal wall is an easier and more satisfactory method of handling the splint catheter, because it permits recording of urine drainage, facilitates irrigation, and provides greater ease of fixation (Figs. 12-18).



Fig. 9.

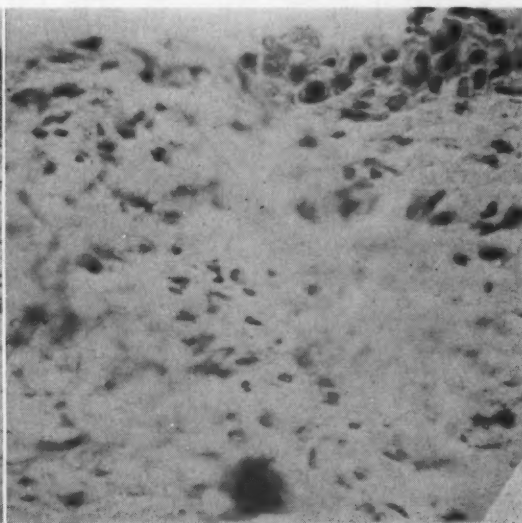


Fig. 10.

Fig. 9.—Low-power photomicrograph of regenerated ureter. See Fig. 8.

Fig. 10.—High-power photomicrograph showing regeneration of tissue. See Fig. 8.

When urinary diversion is required, the same principles are employed. Catheters (polyethylene) are brought out through the colostomy or rectum in intestinal transplants, and through a suprapubic wound in the bladder reconstruction operation.

It is not the purpose of this report to present a statistical analysis of a large series of cases, since the majority of ureteral injuries on this service have been deliberate and involve some form of urinary diversion which will be the subject of a subsequent report. During the past 5 years, however, only 3 nephrectomies have been necessary for ureteral injuries of all types.

#### Comment and Review of the Literature

A review of the literature on this subject is fraught with danger, so voluminous has it become and so varied in its scope and details.

*Prophylaxis.*—There are numerous clinical articles<sup>8-34</sup> dealing with the incidence of these lesions, methods of prevention, technique of repair, etc.

While much is written of the need for preoperative ureteral catheterization, little effort is directed to the in situ recognition and detection of the injury when suspected. The more frequent employment of dissection of the broad ligament with identification of structures (vessels and ureter) rather than mass clamping and ligation will obviate most of the accidental injuries.

We concur with Benson and Hinman<sup>8</sup> on the importance and mechanisms of prophylaxis and the in situ detection of such injuries. It is our opinion that the greatest deficiency is a failure to explore the retroperitoneal space, ureteral tunnel, and bladder base when extensive dissection has been necessary. In general, young gynecologic surgeons are poorly equipped by experience to dissect out and trace a ureter to be certain it has not been injured.

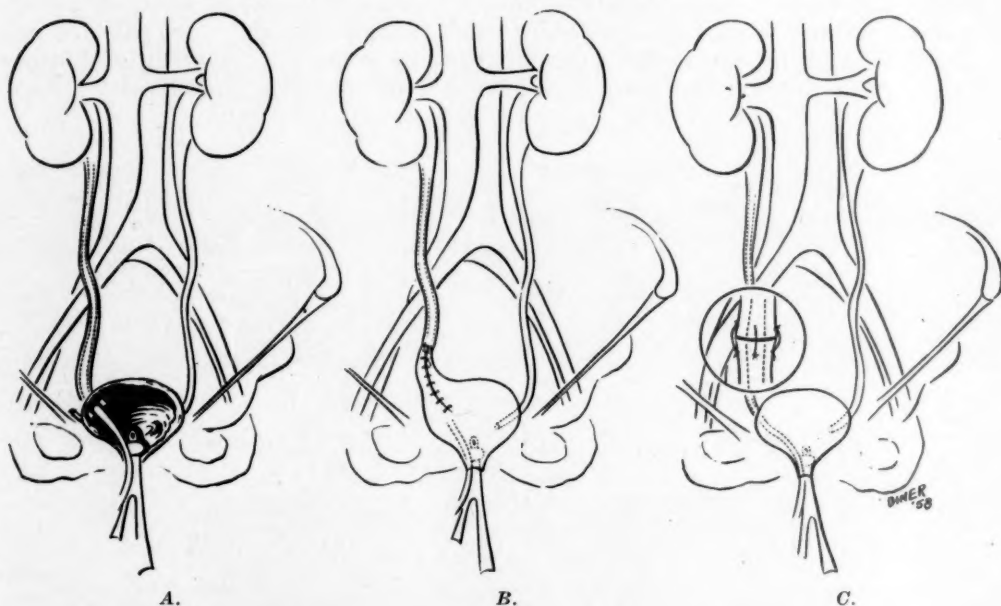


Fig. 11.—Diagrammatic sketch of available procedures for ureteral repair. A, Uretero-cystostomy. B, Bladder graft. C, Ureteroureteral anastomosis. All supported with polyethylene catheters for from 14 to 28 days.

To obviate this, each resident on our service is instructed in and personally conducts exposure and survey of the ureters to insure familiarity with this surgical anatomy. At times, the use of intravenous dyes is of help in locating injuries. Exploratory linear incision of the bladder or ureter with the passing of a catheter is a useful device and, though repugnant to the gynecologist, is both safe and effective.

While the prophylaxis discussed above will do much to reduce accidental injury, the anatomic distortion of major disease will occasionally result in such accidents. For these, and the deliberate or secondary ischemic injuries, certain data from our studies and the literature might improve results.

**Choice of Technique.**—Whether the injury is discovered at the time of initial operation or subsequently, there are three basic techniques available for the repair—ureteroureteral anastomosis, ureterocystostomy, and ureteral grafting. The choice of these appears to be determined by the magnitude and location of the ureteral defect.

In the lower or terminal ureteral injuries usually found in gynecologic surgery for benign disease, grafting is seldom necessary. Simple bladder

reimplantation is most useful for juxtavesical injuries. If the injury is somewhat more distant, ureteroureteral anastomosis is to be preferred, unless the defect is such as to preclude its use. Under these circumstances, ureteral regeneration or ureteral grafting must be employed.

### Factors Influencing Healing

*Tissue.*—Many factors have a bearing on the healing of such anastomoses. Our observations are in agreement with those of Masterson,<sup>35</sup> that compromised

Fig. 12.  
BLOCK DISSECTION FOR  
CARCINOMA OF THE CERVIX.

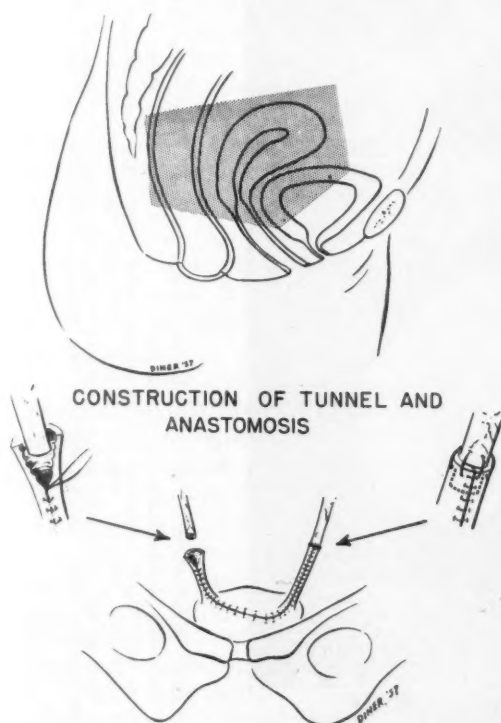
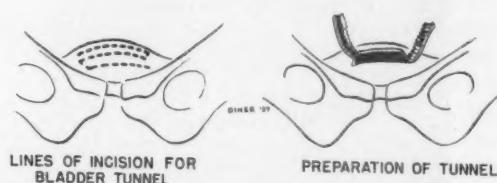


Fig. 14.

Fig. 13.



RECONSTRUCTED  
URINARY AND RECTAL TRACTS

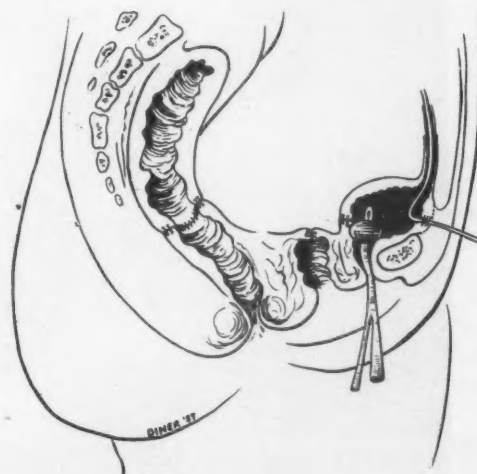


Fig. 15.

Figs. 12, 13, 14, and 15. Schematic diagrams of the technique for block resection in residual carcinoma of the cervix, with bladder reconstruction and bilateral bladder tube graft.

tissues heal poorly (irradiated, traumatized, devascularized, and/or uriniferous). Hinman and associates<sup>36-39</sup> have also reported interesting experiments dealing with some of these items. While we have had no experience with the suggestions by Lapides and associates<sup>40</sup> that a layer of fat facilitates healing, we have observed that a carefully preserved peritoneal flap attached to the anastomosis is of great value.

*Cortisone.*—While others may have had favorable results with cortisone, we were unable to find confirmatory reports of Baker's<sup>4, 5</sup> observations in the literature nor were we able to confirm these observations in our own experiments.

*Technique.*—The mechanics of anastomosis have involved several minor variants, all designed to minimize stricture formation. The use of oblique



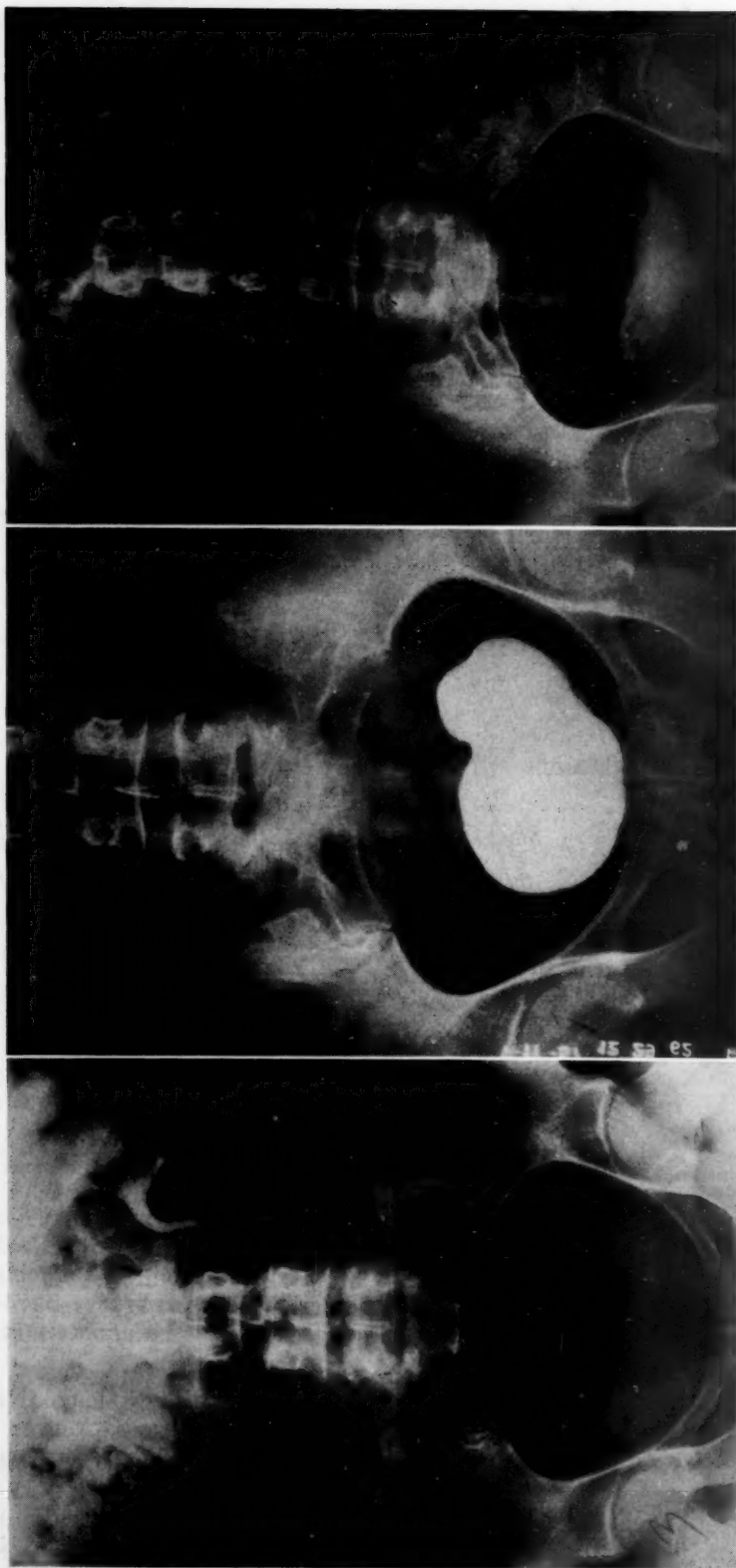


Fig. 16.

Fig. 17.

Fig. 18.

Figs. 16, 17, and 18.—Radiographs of Patient M. F., No. 12-29-62, with radiation residual carcinoma of the cervix.  
 Fig. 16.—October, 1956. Shows almost complete nonfunction of right kidney. On cystoscopy, there was invasion of the bladder base.  
 Fig. 17.—See Fig. 16 for history. Patient had block resection of carcinoma including both ureters and bladder base in December, 1956. Radiograph is cystogram in January, 1957, showing bladder distortion but adequate regeneration and no ureteral reflux.  
 Fig. 18.—See Fig. 16 for history. This radiograph is intravenous pyelogram in July, 1958 (16 months after reconstruction). Note bladder distortion persists but left kidney is functioning well. Right kidney has become nonvisualized and probably nonfunctional. Patient is free of evidence of residual carcinoma.

cuts across the ureter was thought to provide a larger stoma. Likewise, the spatulated closure described by Nesbit<sup>41</sup> and further reported by Sayegh<sup>42</sup> appears sound.

Perhaps the most significant recent development has been the mucosal approximation technique of Cordonnier.<sup>6</sup> This appears to provide more rapid healing of the mucosa, and since the fibromuscular regeneration follows the mucosa, the scar is minimized and stricture formation limited.

While subscribing to the principles of mucosa-to-mucosa anastomosis, we have tended to a loose approximation of freshly severed ends, over polyethylene splint catheters.

*Suture.*—The role of sutures is difficult to evaluate. Our own experiments suggest that in ureteroureterostomy sutures are not necessary, and our clinical experience using minimal sutures (we have not had the courage of our conviction to eliminate them entirely) tends to confirm this. The several reports in the literature on sutures such as that of Maluf and Halpert<sup>43</sup> are confusing, for they combine various types of sutures with various types, sizes, and duration of splint catheters. All authors agree that fine No. 4-0 or 5-0 chromic sutures are to be preferred to nonabsorbable material. Our experience suggests that loose approximation without tension with minimal suturing is adequate and offers least interference with healing.

*Catheter Splints.*—Although catheter splinting and drainage have been extensively studied, the issue is far from clear because of the many variables. The report by Weaver<sup>14</sup> purporting to compare the results of large and small catheters in reality is comparing two types of catheters, woven French and polyethylene.

The first use of polyethylene as indwelling material is obscure. From a review of the literature, it appears that this material was studied simultaneously by the surgical staff of the Mayo Clinic by Grindlay and associates<sup>45-47</sup> in thoracic duct and tracheobronchial studies in dogs in 1946, in neurosurgery in 1947, and in urology in 1948, and by Ingraham and associates<sup>48, 49</sup> in Children's Hospital in Harvard in 1946 and 1947.

In all probability, the introduction of this substance will require a reappraisal of the data on catheter splinting of the ureter. Our experience suggests that snug, but not large, polyethylene catheters not only fail to incite inflammatory reaction, but prevent stricture formation and promote epithelial and muscle regeneration in the repair process.

The literature on the duration of catheter splinting seems to offer more uniformity. Cordonnier and Roane<sup>50</sup> observed that with x-ray ureteral catheters little evidence of inflammatory change appears until after 3 to 4 weeks, and they concluded that 4 weeks is approximately the optimum duration of intubation. These observations are confirmed in part by our own experiments reported here, and by the studies of Aberhart,<sup>51</sup> Maluf,<sup>43</sup> Kimbrough and associates,<sup>52</sup> Kelley,<sup>53</sup> Brunschwig and Pierce,<sup>54</sup> and Benson.<sup>8</sup> Davis,<sup>55</sup> in a recent extensive review of catheter splints, suggested that polyethylene splints are valuable in transections of the ureter, and should be indwelling for 4 weeks.

In our experimental studies and clinical observations, 21 to 28 days appears to be the desirable duration of intubation with polyethylene catheter splints. We have had no experience with the T-tube splinting of Aberhart,<sup>51</sup> but have found the suprapubic cystotomy exit a feasible and effective method of clinical management.

### Clinical Repair

*Ureterocystostomy.*—Our experience is in agreement with that of Warden and Higgins,<sup>56</sup> Rubin and Goldstein,<sup>57</sup> Grey and associates,<sup>58</sup> and Weaver,<sup>59</sup>

that good results are obtained by reimplantation into the bladder and the employment of fixation and polyethylene splints for 21 to 28 days.

*Ureteroureteral Anastomosis.*—When the injury is more distant but without significant loss of tissue, we have employed simple end-to-end approximation of the freshly severed ends, loosely approximated with fine chromic catgut sutures over polyethylene tubes. This technique is simple and when the catheter splints are left indwelling for 21 plus days, good results have been obtained.

*Ureteral Regeneration.*—When the ureteral injury has resulted in a significant defect, other methods of restoring the urinary continuity must be employed. Hinman and associates<sup>8, 36-39</sup> have conducted extensive experiments on ureteral regeneration and conclusively show that under favorable conditions both the muscle and epithelial layers of the ureter will regenerate. These observations have been confirmed by Trautner and Raaschou,<sup>60</sup> Lapidès and Caffery,<sup>40</sup> Hamm and Weinberg,<sup>61</sup> Boyarsky and Duque,<sup>62</sup> and by the studies here reported. Huffman and associates<sup>63</sup> resected 5 to 6 cm. of mid-ureter and failed to observe regeneration. Whether this difference is due to the location or size of the defect is unknown. Davis,<sup>55</sup> in a recent review of the question of regeneration, takes issue with these concepts and doubts that muscle regeneration takes place in transected ureters. Our observations and those of others suggest that 2 to 3 cm. of the terminal ureter will regenerate in approximately 4 weeks.

*Grafting.*—When the defect is great and precludes ureteroureteral anastomosis, ureterocystostomy, or regeneration, some form of grafting or diversion is necessary. Many prosthetic, homologous, heterologous, and autogenous structures have been employed (Hardin,<sup>64</sup> artery and polyethylene; Drinker,<sup>65</sup> calf ureter; Sewell,<sup>66</sup> freeze-dry artery; Schein and associates,<sup>67</sup> artery; Schein and associates,<sup>68</sup> Fallopian tube; Horton and Politano,<sup>69</sup> skin grafts; Rosenbert and Dahlen,<sup>70</sup> vein; and a great many authors,<sup>71-86</sup> ileum).

In 1893, Van Hook<sup>87</sup> and subsequently Boari<sup>88</sup> in 1894, described the preparation of a pedicle graft from the bladder. This procedure has been reported recently by Landsteiner,<sup>89</sup> O'Heeron and associates,<sup>90</sup> Barnes and Farley,<sup>91</sup> Caughlan,<sup>92</sup> Henderson,<sup>93</sup> Lewis and Cletsoway,<sup>94</sup> Dunfield,<sup>95</sup> and Boyd.<sup>96</sup>

Our own experience in grafting has been principally in the repair of the deliberate ureteral injuries in extensive surgery for residual (postradiation) carcinoma of the cervix. Here we have employed a bilateral bladder tube graft for ureteral repair in bladder reconstruction with good results (Figs. 12-15). It has been possible to develop grafts of 3-5 cm. which can bridge major defects of the terminal ureter. The grafts are constructed with No. 4-0 chromic catgut over polyethylene tubing and the ureter is anastomosed to the end of the graft.

### Summary

Ureteral injuries have been classified as accidental, deliberate, and secondary ischemic. Our clinical experience suggests that all three types are increasing in frequency.

The major factor in the prevention of the accidental injuries is better trained gynecologists, especially with experience in exploration of the ureters at the time of operation.

Tension, compromised tissue (blood supply, radiation, and urinary extravasation), inadequate fixation (splinting), and infections unfavorably influence healing of the urinary tract.

The repair of ureteral injuries is favorably influenced by loose approximation with minimal suture over polyethylene catheter splints left indwelling for 3 to 4 weeks.

Ureteroureteral anastomosis and ureterocystostomy provide the best results for minor defects in the terminal ureter. Bladder tube grafts are preferable for major defects in the terminal ureter.

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We also wish to express appreciation to Merck & Co., Inc., Rahway, N. J., for the generous supply of cortisone used in these experiments.

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### Discussion

DR. MICHAEL J. JORDAN, New York City.—The inadvertent injury to bladder or ureter in the course of gynecological procedures has always been a source of worry to the pelvic surgeon. In former years, the repair of these injuries was frequently approached with a sense of apprehension and sometimes uncertainty. Today, in the solution of major pelvic problems, operations on the urinary tract are often important and necessary to obtain a successful end result. This is particularly true with the present trend toward extensive and ultraradical pelvic surgery in the treatment of pelvic malignancies. The degree of success of these operations will depend to a great extent on the ability of the gynecologic surgeon to manage the problems and complications involving the urinary tract.

I should like to emphasize several important points in the prevention and management of urological injuries and urinary diversions. One must differentiate between urinary tract injuries that occur during operations for benign conditions—for the most part avoidable injuries—and those sustained during radical surgery. The latter are sometimes inevitable because of the nature of the disease and the surgery required. In radical hysterectomy with contiguous pelvic node dissection, the accepted incidence of fistula or ureteral injury is 7 to 10 per cent. With radical surgical treatment after failure of irradiation, the incidence of genitourinary complications is doubled or tripled, mainly because of devitalization of tissues brought about by ischemia and fibrosis.

The neoplastic processes we are particularly concerned with are in the lower half of the pelvic ureter, since a malignancy that has extended beyond Stage I into the broad ligament usually involves the ureter or causes obstruction at a point 4 to 6 cm. above the interureteric ridge. Here the ureter crosses into the broad ligament, and the uterine artery crosses the ureter. Extension of the neoplasm into the anterior vaginal wall will cause involvement or obstruction of the ureter near its junction with the base of the bladder, a distance of 1 to 1.5 cm. above the ureteral vesicle orifice. Thus, in the preoperative evaluation of the patient with carcinoma of the cervix, cystoscopy, catheterization of the ureters, renal function tests, retrograde and/or intravenous urograms are helpful in selecting the proper surgical procedure. Depending on the extent of involvement, the choice of operation may range from radical hysterectomy with pelvic node dissection to total pelvic exenteration.

If a ureterocystostomy or ureteroureterostomy has been done, a properly placed, fixed, and managed ureteral polyethylene catheter must be left in place for an adequate period of time ranging from 2 to 4 weeks. Suprapubic cystostomy too is indicated for the protection of the anastomosis and for better control of the polyethylene catheter or catheters. I am in complete agreement with Dr. Brown's use of polyethylene tubes and fine sutures. Nonabsorbable sutures should be avoided and if used should not be in contact with mucosa of either the ureter or the bladder. The rule should be fine absorbable sutures, good approximation, and not strangulation of the tissues.

The use of drains was not mentioned in this paper. Proper drainage is extremely important. A fine latex drain within a drain serves the purpose better than a single drain which collapses readily. It should be placed dependently near but not on the site of repair and should not be removed too soon. Good drainage is far more important than a watertight closure.

The importance of Dr. Brown's presentation is further emphasized in light of the fact that radical surgery is possible today through advances in anesthesiology, antibiotics, fluid and electrolyte balance. This surgery has gone beyond palliation and has justified itself as a curative procedure in well-selected cases. It has given impetus to the surgeon to return the patient to as nearly as possible normal anatomical and physiological states, and these are chiefly dependent on methods of urinary diversion and control. When partial or total exenteration must be done, it is necessary to divert the urinary stream into an isolated or intact segment of bowel that acts as an artificial or substitute bladder.

The disadvantages of additional "ostomies" are well known. Diversion of the urine into the fecal stream, even if the sphincter is intact, gives rise to problems frequently quite serious: ascending infection of the urinary tract, re-absorption of urine with resulting chronic azotemia and hyperchloremic acidosis. When general well-being and survival are more important than the comfort and convenience of the patient, the operation which attains this end should be the one of choice, even though it be bilateral nephrostomy or ureterostomy.

The importance of Dr. Brown's experimental studies cannot be overemphasized. The high morbidity and mortality associated with pelvic surgery can, for the most part, be attributed to the failures or complications of the surgery performed on the urinary tract. Therefore, the solution to the problem is the development of better methods of repair of ureteral injuries and better methods of urinary diversions.

Dr. Brown has shown that the use of cortisone is relatively unimportant and possibly hazardous. A most important conclusion from his experiments or intubation of the ureters is that polyethylene catheters can and must be left in place for a longer time than we formerly thought necessary to permit regeneration of the ureter and prevent stenosis at the point of anastomosis. It is the practical application of these principles that brings about a more successful urinary tract operation. For example, the present status of the artificial bladder leaves much to be desired. However, with advances made possible by such experiments as those presented here, we can look forward to the construction of the ideal artificial bladder which will provide comfort and longevity to the patients who must undergo radical surgery.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—With our present understanding and current surgical therapies for pelvic carcinoma, there will be instances in which it will be necessary to cut across or sacrifice portions of the ureters. In addition to the risks which the authors listed as causes of damage, there may be the direct damage by the malignancy itself. That last item is not under discussion at this time, however. The injured ureters, regardless of the cause, present the problem of re-establishing a normally functioning urinary tract. It is a surprise to us to hear from Dr. Brown that the number of urinary tract injuries is increasing (presumably he means the accidental ones). Except in the instances of extensive resection for malignancies, we do not share his view.

In the last 10 years at the Chicago Lying-in Hospital, 9 known accidental injuries occurred. The repair and management of the injuries in 9 patients belong in the following classifications: (1) two cases, ureteroureterostomy; (2) three cases, ureterovesicostomy; (3) four patients, ligation of the ureters—one transfer to the skin (this patient and 2 others had nephrectomy subsequently and the fourth had the ligation freed before damage occurred). The review of our complications demonstrates that they were, in most instances, the result of inexperience or failure to follow accepted practices for identification of the ureters.

We agree completely with the authors that accidental ureter insults should be reduced. Since infection may be related to healing and fistula formation as well as to scar production, one may ask why only penicillin was used in the experimental study. According to our information, *Escherichia coli* and *Proteus vulgaris* are the two most common urinary tract infections in dogs. Penicillin will not reduce or prevent in the slightest *E. coli* infection. If cortisone is to reduce the amount of scar tissue, then the dosage must be adequate. Others have suggested that appropriate amounts of ACTH might be a better preparation in the minimization of scar tissue. When cortisone or ACTH is used in appreciable amounts or for a moderate time, adequate observations and tests should be made for the patient's protection.

In the human subject a poor result in relation to ureteral injuries is sufficiently serious that one is justified in taking some calculated risk, provided proper precautions are exercised. Dr. Brown has implied that there is not a really good substitute for a ureter or a bladder and with this there can be no disagreement. A number of efforts have been made to design or substitute structures for the bladders. In all instances there are major shortcomings.

The authors' experimental work speaks for itself, but it is known that one cannot be assured that comparable reactions and results will occur in human subjects.

Dr. Brown's summary is consistent, yet one may be critical of his statement that "the major factor in the prevention of the accidental injuries is better trained gynecologists. . . ." A competent gynecologist should know the anatomy of the pelvis. Perhaps the cause is more a matter of lack of precaution during operation. The problem of ureteral injuries and fistulas must be coldly and conscientiously faced.

DR. J. V. MEIGS, Boston, Mass.—If you injure a ureter in doing radical surgery, the anastomosis of this ureter, ureter to ureter, is very unsatisfactory. The anastomosis is not difficult but it does not heal very well. Possibly if we left a polyethylene catheter in longer it might do better. If you injure a ureter when you are doing radical surgery, your best chance of success is to transplant it into the bladder.



We have too many fistulas in our radical surgery for cancer of the cervix. Years ago, Dr. John Sampson, when he was a resident at Johns Hopkins, wrote that, because of the number of fistulas, the ureter had better be deliberately cut and transplanted into the bladder. I am not so sure that he is not right, but I have never had the nerve to do it deliberately. The ureter-bladder anastomoses work well, although I am not advocating that anybody cut the ureter and transplant it into the bladder by the technique that Dr. Brown has described. If we did, however, it is obvious that we would do a very much better removal of tissue around the cervix and vagina.

DR. CONRAD COLLINS, New Orleans, La.—I am wholly in accord with many of the points that Dr. Brown has presented in this superb paper, and I for one want to re-emphasize the idea that residents should be taught what is behind the peritoneum. I have had the privilege of examining on the American Board for many years, and I can say that of some of the candidates they were quite lost in that region.

Second, I think his idea and Dr. Meigs' of deliberately cutting the ureter is a good one. Since Dr. Brown has shown us that you can get results with a tunnel from the bladder, it certainly will make the operation easier and, I think, perhaps more effective.

Our clinical experience with cortisone and its use in preoperative treatment of vaginal fistulas has borne out what Dr. Brown has said. We do not think that in patients to whom we give cortisone we have any more spontaneous healing of bladder fistulas with the catheter in for 10 or 12 days than we had before, but what happens is that the tissues surrounding the fistula come back to nearly normal more quickly. We can then repair that fistula in 2 weeks instead of waiting 6 months, and the surrounding tissues accept dissection, suture, and hold the sutures as they would 6 months later. I am not in accord with some of our endocrinologists and internists who, upon learning that cortisone ointment has been applied to the vulva for a few days, state that this patient should not be operated upon until tests have been made and cortisone given both pre- and postoperatively. In the total dosage that we give (up to 3 Gm.) we do not particularly worry about it and we have not had any deaths as a result.

In the case in which a ureteral fistula develops 8 to 10 days or 2 weeks after operation the repair may not hold if it is done too soon, but a lot of these will heal spontaneously. If a catheter can be passed at cystoscopy, I think we might get a greater number of cases to heal spontaneously, as Dr. Brown has proved experimentally. Sometimes urologists cannot pass a catheter up the proximal end of the ureter, however, and in cases where the fistula has failed to heal spontaneously, cortisone and early repair are utilized.

In patients upon whom we have reoperated to reimplant the ureter into the bladder, we have found the bladder contracted, and I think a good clinical procedure prior to repair is to dilate that bladder daily. This makes the operation much simpler and we can get our tube from the bladder much more easily.

DR. BROWN (Closing).—The only item I should like to belabor is the challenge which Dr. Hesseltine raised regarding better trained gynecologists. I wonder how many of each of your residents intentionally dissect out a ureter from the pelvic brim to the bladder so that they know the anatomy of the retroperitoneal area, and when they are in trouble can then find their way around by prior experience. I am afraid that the gynecologists coming through residencies in our smaller hospitals particularly are poorly equipped by previous experience to know where the ureter is and to be able to find it and to manage its injuries. And unless we train these young men in this surgical anatomy surgical ureteral injuries will continue to increase. It is quite correct, as Dr. Hesseltine has indicated, that most of the injuries with which we were dealing were deliberate ones, but we do occasionally have an accidental one, as I am sure all of you do.

It has been a pleasure to have an opportunity to show some of the data which we have accumulated and to suggest that you try polyethylene catheters and leave them in for four weeks. You may have to tie the urologist's hands to keep him out but it will work.



## THE RELATIONSHIP OF THE CHORION TO THE FETAL LIVER IN NORMAL AND ABNORMAL PREGNANCY\*

EDWARD C. HUGHES, M.D., SYRACUSE, N. Y.

*(From the Department of Obstetrics, State University of New York Upstate Medical Center)*

**T**HE histology of the chorion, the chemical reactions which occur in cellular elements, as well as the endocrine secretions, are not the same during the early formative stage of the embryo as they are during the fetal growth phase. These processes change at approximately the mid-portion of gestation, the alterations being evident in the cellular reactions in the chorion which are related to the functions of the fetal liver. These physiological processes result in the synthesis of essential nutriments for the intrauterine growth and development of the fetus. Fetal survival with sound development depends upon this relationship which becomes more defined as pregnancy advances.

This presentation will discuss some of the cellular reactions of the chorion as they relate to the activity of the fetal liver, as an example of the interrelationship of the chorion and one organ of the fetus. Studies also have been conducted on patients with complications of pregnancy, such as toxemia, isoimmunization, diabetes, and recurrent prematurity. To show this relationship, the metabolism of glucose has been demonstrated by histochemical methods in the cells of the chorion and the fetal liver at various stages of pregnancy.

We have arbitrarily divided these metabolic phenomena into three phases:

*Phase I.*—The stage of preparation. This stage occurs during the normal menstrual cycle when glucose is stored in the endometrial glands from the day of ovulation until a few days before the onset of menstruation. Alkaline phosphatase, perhaps concerned with the polymerization of glucose, is found during the secretory phase of the cycle at the periphery of the endometrial glandular epithelium and in the endothelial cells of the spiral arterioles. Glycoproteins are also found in the glandular epithelium at this time. Satisfactory implantation of the blastocyst is influenced by successful metabolism of these substances.

*Phase II.*—This phase begins with the day of implantation and continues until the one hundred twentieth day of pregnancy. We have chosen the one hundred twentieth day as the end of this phase because several specimens have indicated a change in function at this particular time.

\*Presented at the Sixty-ninth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Va., Sept. 4-6, 1958.

*Phase III.*—This includes the time from the one hundred twentieth day of pregnancy until term, during which time constructive changes in the body of the growing fetus take place.

### Materials and Methods

Special histochemical staining methods have been used which are designed to demonstrate the presence of glycogen, alkaline phosphatase, and mucopolysaccharides. The following staining methods were employed: (1) the Best carmine stain was used for glycogen determination; (2) a modification of the Gomori stain at a pH of 9.4 was used for the alkaline phosphatase; (3) the stain of McManus and PAS stain were used to demonstrate the mucopolysaccharides and collagen material; (4) a special preparation of Masson and alkaline phosphatase stain were used to demonstrate nuclei and chromatin material.

Three groups of patients have been studied in this manner. Group I provided specimens of products of conception which were obtained from 10 normal patients ranging from the twenty-fourth day from ovulation to the fortieth week of gestation. The chorion and fetal livers studied in this group were obtained in cases of therapeutic abortion by hysterotomy and hysterectomy and two specimens after postmortem cesarean sections. Group II, analyzed in a similar manner, included 45 patients with placental complications. Group III consisted of 75 patients whose placentas alone were analyzed by the above-described methods. Both of the latter two groups had pregnancy complications such as toxemia, isoimmunization, diabetes, and recurrent prematurity. Twenty-six of these patients, equally divided between Groups II and III, had quantitative determinations of the excretion of chorionic gonadotrophin and pregnandiol in the urine during the pregnancy.

Further controls for glycogen staining were made from specimens of heart and diaphragm muscle in the same fetus and were stained simultaneously with the liver sections. Numerous normal placentas have been studied with similar staining methods.

### Histochemical Study of Chorion and Fetal Liver During First Half of Pregnancy

Although we have divided the metabolism of glucose into three phases, Phase I will not be discussed because most of the histochemical and histological changes which occur in the endometrium at this time have been described previously.

*Chorion.*—During Phase II, the chorion appears to be more important from a functional standpoint than the developing embryo itself. At this time all of the important organs of the embryo are undergoing development and differentiation. Little, if any, individual specialization of function is going on at this time. There appears, however, to be an active synthesis and storage of glucose as glycogen in the cells of the chorion, while the fetal liver itself shows no effort to carry on the process of glycogenesis.

The main structures of the chorion are the syncytium or the syncytial trophoblast and the cytotrophoblast or the Langhans cells. The former type of fetal cells are permanent cells of the chorion and continue to function throughout pregnancy. They are in juxtaposition to the maternal decidua and are the outer covering of the chorionic villi. These cells constantly produce the enzyme alkaline phosphatase, the amount secreted increasing steadily as pregnancy progresses. Whether this enzyme has much to do with the transfer of glucose or other substances from the decidual sinuses to the fetus

is not definitely known. Many tiny villi appear on the outer edge of the syncytium which makes the brush border which persists throughout gestation and which apparently increases their absorptive power (Figs. 1 and 2).

The cytotrophoblasts or Langhans cells, which are the inner layers of cells covering the villi during early gestational days, are variable in their

Fig. 1.

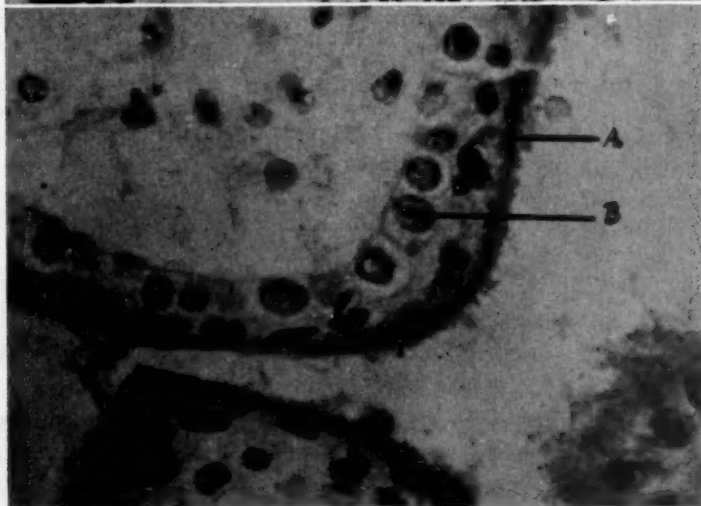
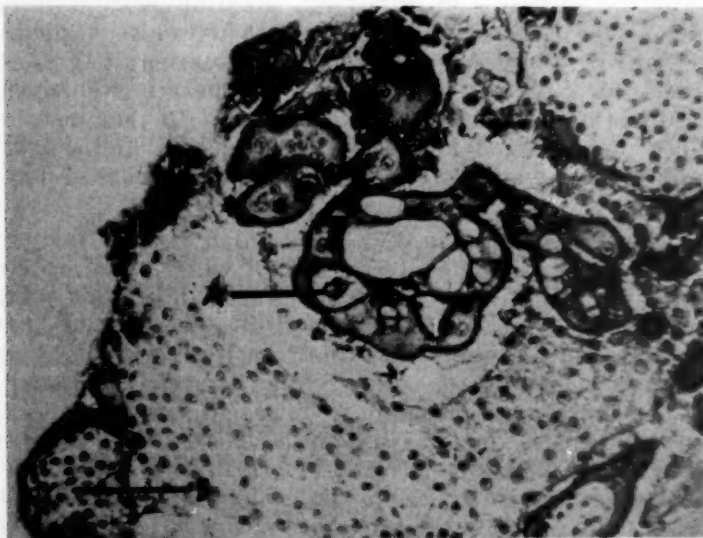


Fig. 2.

Fig. 1.—Ovum 24 days old. Low-power view of the terminal ends of the chorionic villi and decidua. The section is stained for alkaline phosphatase by the Gomori technique. A, Syncytial cells secreting large quantities of alkaline phosphatase. B, Large numbers of cytotrophoblasts (Langhans) showing no alkaline phosphatase. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

Fig. 2.—Ovum 24 days old. High-power view of chorionic villi stained for alkaline phosphatase by the Gomori technique. A, Syncytium—note large quantities of alkaline phosphatase at the margin of the cells and dark staining nuclei; note the brush border with alkaline phosphatase. B, Cytotrophoblasts (Langhans)—primitive cells which do not produce alkaline phosphatase and which are not found in this location in the chorion after the middle of pregnancy. ( $\times 600$ ; reduced  $\frac{1}{2}$ .)

persistence and have several important functions. The original cytotrophoblasts appear in the previllous ovum but become differentiated and transformed as pregnancy advances toward term. The primitive cytotrophoblast

secretes chorionic gonadotrophin soon after implantation and metabolizes glucose from the decidua storing it as glycogen until about the tenth week of gestation (Figs. 3 and 4). At first these cells line the villi, being in close approximation to the syncytium. Later, they disappear from these locations,

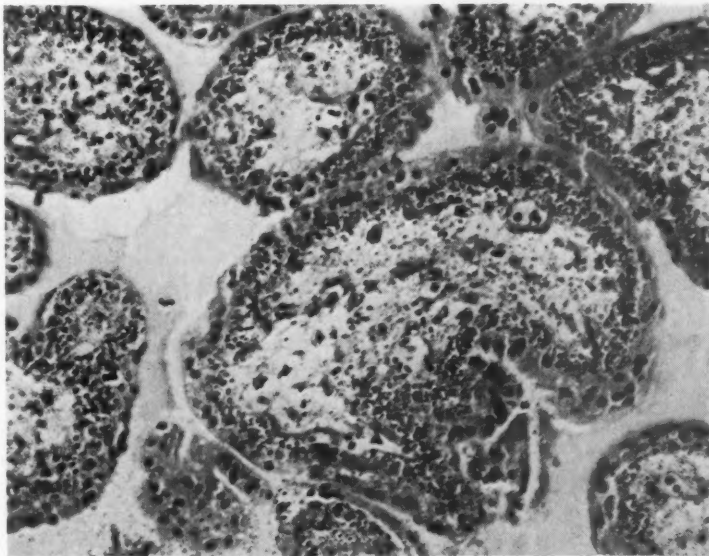


Fig. 3.—Ovum 24 days old. This low-power section of several chorionic villi stained by using periodic acid-Schiff stain shows large quantities of glycogen. This is indicated by the black dots deposited in the cytotrophoblast cells of the villi. Syncytium does not store glycogen. ( $\times 140$ ; reduced  $\frac{1}{4}$ .)

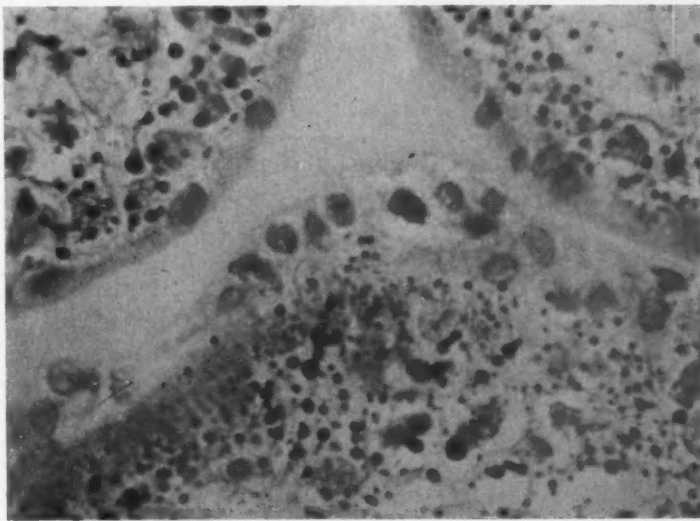


Fig. 4.—Ovum 24 days old. Periodic acid-Schiff stain. This high-power view of 3 chorionic villi demonstrated the glycogen deposition in the cytotrophoblasts (Langhans cells). Syncytium shows no glycogen. ( $\times 600$ ; reduced  $\frac{1}{4}$ .)

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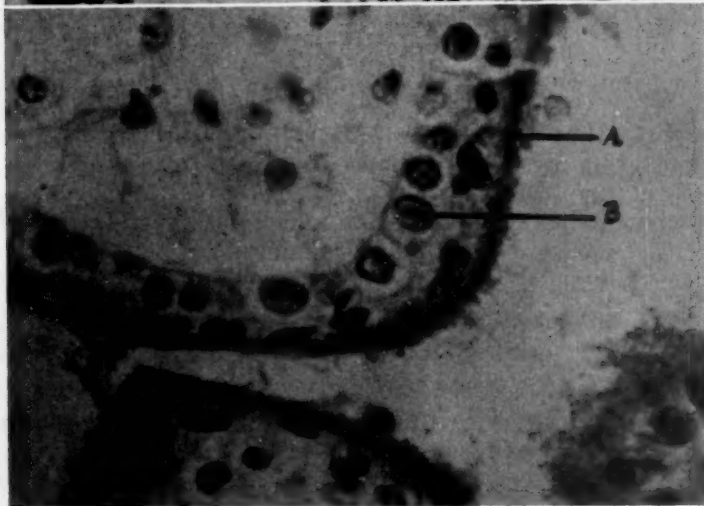
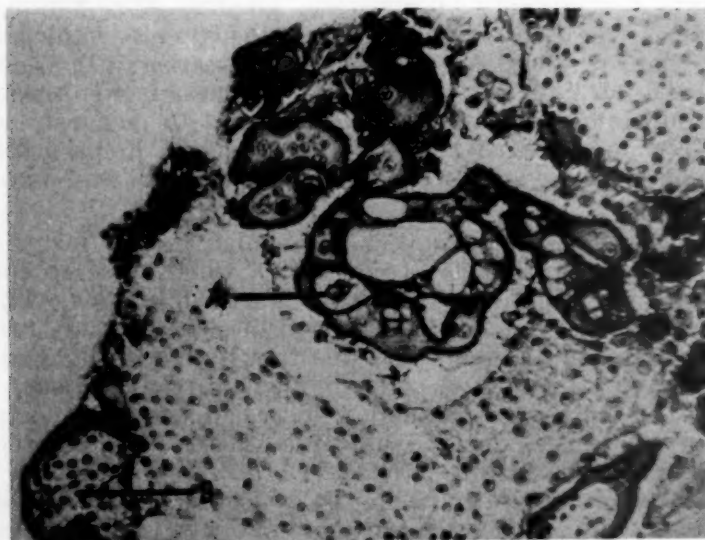


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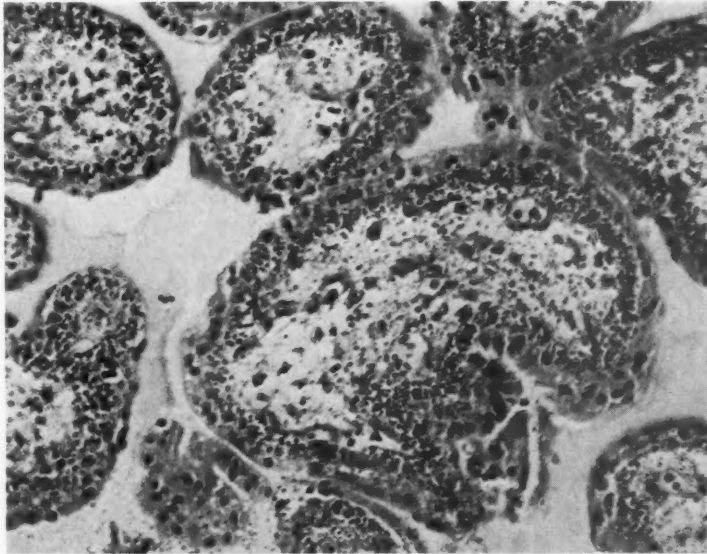


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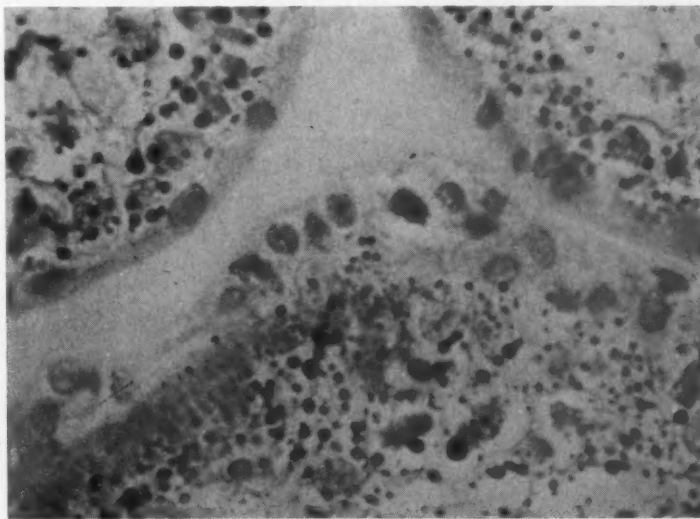


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the decidua and help to form the intervillous spaces but continue to metabolize glucose (Fig. 5). These cells remain until approximately the mid-portion of pregnancy when they are altered histologically and functionally. Some cytotrophoblasts are noted in the mature placenta at the placental plate but their number is relatively small. The important functions of these cells during this phase of gestation are to furnish nutrition for the embryo and to secrete chorionic gonadotrophin.

**The Fetal Liver.**—During the first portion of gestation the fetal liver does not carry on the process of glycogenesis. The liver cells become arranged into the usual histological patterns at about the tenth week and enter into the beginning development of the hemopoietic system. Erythropoiesis starts in the liver at this time and continues during the next 6 to 7 months of gestation. Histochemical staining of the liver shows that there is no glycogen storage at this time, but there is a small amount of alkaline phosphatase secreted at the periphery of the liver lobules and in areas of erythrocyte and erythroblast formation. Histochemical staining of the entire embryonic body at 10 weeks indicates that there are considerable amounts of alkaline phosphatase in the tissues of the mouth and upper esophagus, the bone marrow of the sacrum, and the tubules of the kidney. This early production of alkaline phosphatase, together with the erythropoiesis that has occurred in the fetal liver, is probably the first indication of beginning bone marrow function.

The first half of gestation, designated as Phase II, is one where the chorion assumes the leading role in the absorption of glucose from the secreting decidua and converts and stores it as glycogen in the cytotrophoblasts. This process is probably initiated and maintained by the action of chorionic gonadotrophin. Estrogen and progesterone from the corpus luteum maintain the metabolic activity of the decidua. The fetal liver, on the other hand, does not carry on the process of glycogenesis but is producing the blood-forming units, namely, erythrocytes, erythroblasts, and other constituents of the early blood. Whether the fetal liver enters into the metabolism of chorionic gonadotrophin at this time is not known but speculation leads to the contrary conclusion (Figs. 6 and 7).

### Histochemical Studies During the Latter Half of Gestation

**Chorion.**—The latter half of gestation has been designated as Phase III and extends from the one hundred twentieth day until term. During this time histochemical stains reveal that the functions of the chorion and the fetal liver are reversed. Specimens studied at the one hundred twentieth day of gestation suggest that the change occurs at this time, although the exact time of this conversion may vary from patient to patient. Marked increase in the general metabolic activity of the patient also occurs now.

The syncytial layer of the villi becomes extremely thin, allowing the blood capillaries to come in closer contact with the maternal decidua so that the villi seem to be enclosed in this thin syncytial layer. This development creates

Fig. 5.—Chorion and decidua from 110-day-old ovum. Best carmine stain for glycogen. A, Cytotrophoblasts contained some glycogen protruding from the distal end of the villi, approximating an endometrial gland beginning to line an intervillous space. Syncytium contains no glycogen. B, Endometrial gland containing glycogen. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

Fig. 6.—Ovum 24 days old. Periodic acid-Schiff stain. Liver stained for glycogen. Note lack of liver cell arrangement with lack of glycogen deposition. A, Primitive erythrocyte. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

Fig. 7.—Seven-month normal gestation. Chorion and decidua stained for alkaline phosphatase with modified Gomori stain. A, Decidua with large decidual vessels. No alkaline phosphatase noted. B, Chorionic villi with large amount of alkaline phosphatase secreted by syncytium. Only occasional cytotrophoblasts noted. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

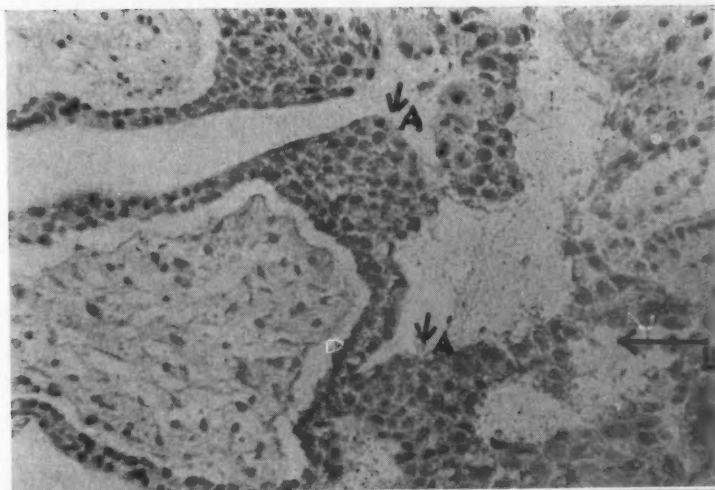


Fig. 5.

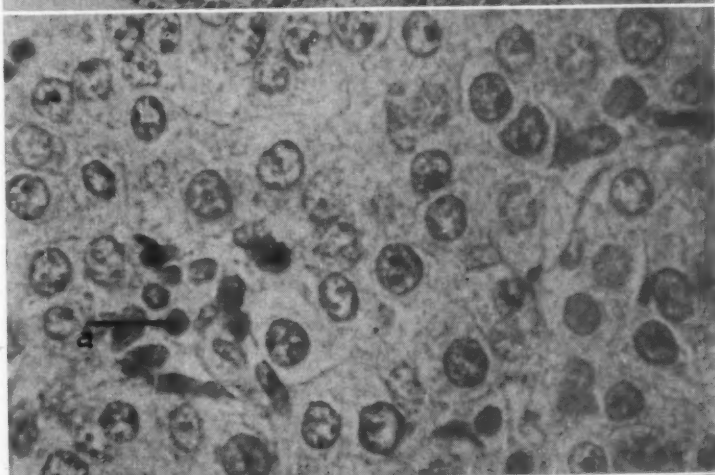


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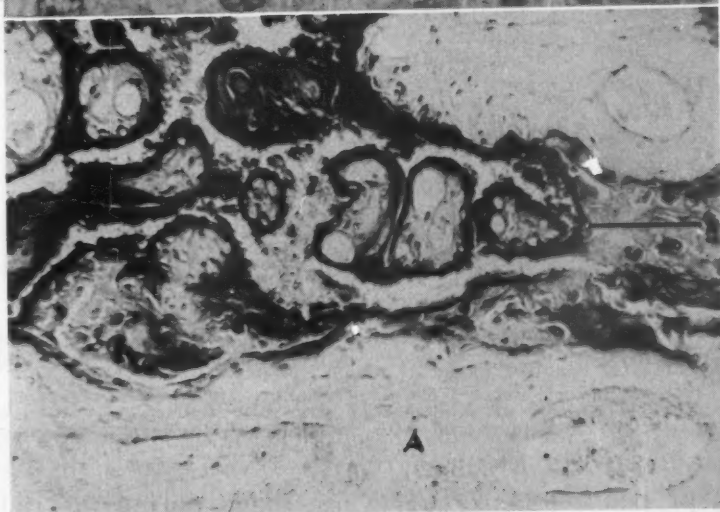


Fig. 7.

Figs. 5-7.—For legends see opposite page.



better conditions for the exchange of oxygen, carbon dioxide, and other necessary constituents of nutrition. The brush border of the syncytium is more prominent and aids in the exchange process.

The syncytial trophoblast continues to secrete increased amounts of alkaline phosphatase, which probably accounts for the increased maternal

Fig. 8.

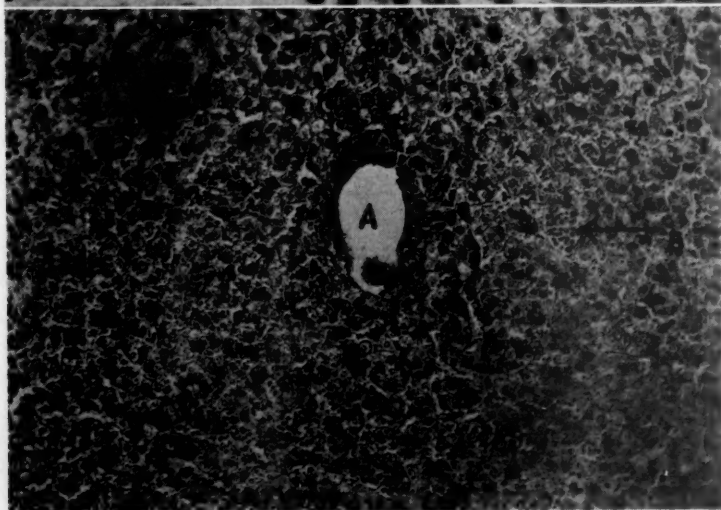
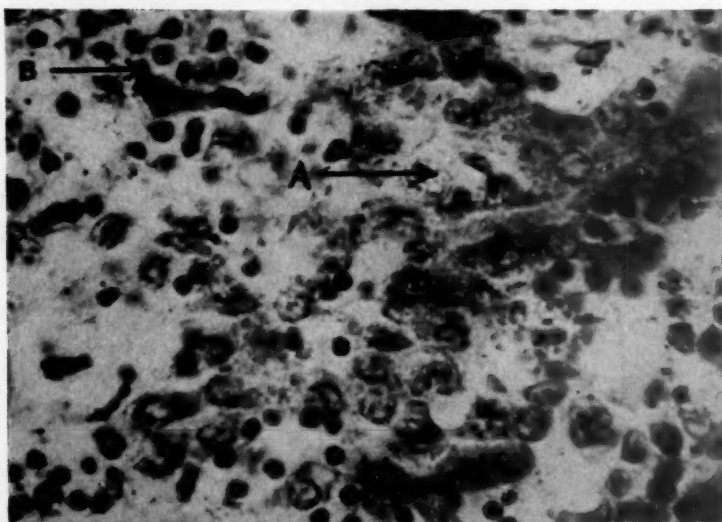


Fig. 9.

Fig. 8.—Liver from normal fetus at 120 days' gestation. Best carmine stain. A, Liver cells with large quantities of glycogen demonstrated in granular form in cytoplasm of cells. B, Primitive erythrocytes denoting moderate amount of hemopoiesis.

Fig. 9.—Liver of normal fetus. Term pregnancy. Best carmine stain for glycogen. A, Central vein. Note orderly arrangement of liver cells. Dark areas indicate large deposits of glycogen which stain deep red with carmine. B, Occasional areas of hemopoiesis. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

blood levels of this substance, which are found during the last trimester. (Fig. 7.) The function of this enzyme may be twofold: (1) it may play an active part in the blood-forming activity of the bone marrow and the liver; (2) it may enhance the transfer of glucose by aiding in its polymerization

during transfer from the decidua to the fetal liver. The syncytium produces and secretes estrogen and progesterone although no proof has been given that these cells are sole producers of these steroids. A rather definite thickening of the syncytium appears as the placenta ages, which may retard the perfusion of substances across its barrier.

The fate of the cytotrophoblasts is different. These cells have a variety of functions during the gestation. The basic cytotrophoblasts disappear at about the one hundred twentieth day of gestation and only an occasional cell can be noted in the stroma of the villi. Additional cytotrophoblast, apparently originating from these primitive cells, is found at the tips of the villi and tends to anchor these structures to the decidua. Wislocki<sup>2</sup> has demonstrated that this cellular trophoblast occurs in column, is found at the placental site, and remains throughout the last phase of gestation. He has also described islands of cytotrophoblast which may penetrate into the myometrium. The original function, storing glucose as glycogen and secreting chorionic gonadotrophin, does not normally persist to this time. A few cells can be found in the stroma of the villi, which accounts for the small amount of chorionic gonadotrophin in the urine during normal pregnancy. However, these cells do not store glycogen at this particular time. A few granules of glycogen may be noted about the large vessels in the large main stem villi.

Areas of infarction, found particularly at the circumference of the placenta, have shown some rather interesting histochemical changes. The syncytial cells have degenerated at this location while the cytotrophoblast reappears in moderate amounts. The deposition of glycogen occurs in these cells and in some of the connective tissue cells. McKay<sup>1</sup> and his group have indicated that this reversal is the result of cellular anoxia. It would appear that the syncytial trophoblasts are the important cells of the chorion at this time and that their function is mainly, aiding transfer of substances to and from across the placental barrier.

*The Fetal Liver.*—The process of glycogenesis begins in the fetal liver about the one hundred twentieth day of pregnancy and the amount of storage of this substance increases gradually until term. It is found in the substance of the liver cells particularly about the central vein. Extramedullary hemopoiesis continues to a moderate degree until approximately the last 2 months of gestation when the number of erythroblasts and erythrocytes decreases (Fig. 8). The amount of alkaline phosphatase secreted by the liver cells during this phase of pregnancy is markedly decreased and only a moderate amount can be demonstrated about the central vein in the normal patient. Increased glycogen storage with diminishing production of erythroblasts seems to be the normal metabolic trend of the liver as pregnancy continues to term. The metabolism and storage of glucose and the release of it into the bloodstream for use by the fetal brain is perhaps the most important physiological function of the fetus at this time (Fig. 9).

#### **Histochemical Analysis of the Chorion and Fetal Liver in Abnormal Pregnancy**

*Chorion.*—Histochemical staining of placentas and fetal livers in patients whose pregnancies have been complicated by toxemia, Rh isoimmunization, diabetes, and, in some cases, by recurrent premature birth, has indicated that there is a disturbed metabolic relationship between these structures. This abnormal relationship is demonstrated by the following evidence:

1. There is a reappearance of increased numbers of cytotrophoblasts of the earlier type.

2. Cytotrophoblasts of the original type reappear in the stroma of some of the villi and occur as sheets of cells throughout the placenta.

3. Glycogen reappears in the form of large granules in these cytotrophoblasts, particularly in the areas of infarction. There is also an increased amount of glycogen about the vessels of the main stem villi and in some cases it may extend even to the smaller villi. Many of these cytotrophoblasts are larger in size and the nuclei are extremely hyperchromatic.

4. Other noteworthy findings are areas of fibrinoid degeneration or deposits of a mucopolysaccharide nature within or without the villi. In some instances this substance may completely surround the villi shutting them off from blood supply and causing anoxia at this local area.

5. In these areas of degeneration, the syncytial trophoblast becomes necrotic, partially disappears or at least loses its histological identity. Alkaline phosphatase secretion continues, however, but appears to be in decreased amounts not only in the areas of degeneration but also in other areas where the syncytium seems to be quite normal.

6. There is an accumulation of fluid in some villi, distending them and causing a disappearance of the blood vessels. Thickening of the walls of the capillaries occurs in some areas when changes of this type are noted (Figs. 10-12).

*The Fetal Liver.*—Histochemical study of the fetal liver of infants who were born when the complications mentioned above were present gave interesting findings. Although one must be careful in evaluating these, significant histochemical changes occurred in this organ: (1) the liver increased in size and weight; (2) the fetal liver was depleted of its glycogen where placental degeneration had been developing; (3) extramedullary hemopoiesis increased in extent as the glycogen concentrations were reduced; (4) the liver in some Rh-negative patients who had been sensitized accumulated considerable quantities of bile pigments with less glycogen.

Decreased liver function, it is believed, is a result of alterations in placental function indicated by the described histological and histochemical changes. This phenomenon has been noted particularly when a pathological process has been of long standing, such as prolonged toxemia, diabetes, and isoimmunization, where antibody titers have been increasing, and where there has been an increase in the excretion of chorionic gonadotrophin in the urine (Fig. 13).

### Hormone Changes

In normal patients the excretion of chorionic gonadotrophin in the urine rises steadily until about the fiftieth day of gestation and then diminishes, but remains in constant small amounts until term. There may be a slight rise prior to the onset of labor. Increased amounts of chorionic gonadotrophin in the urine have been found in 26 abnormal cases including patients with

Fig. 10.—Placenta from patient with toxemia of pregnancy (pre-eclampsia). Best carmine stain for glycogen. *A*, Several chorionic villi show loss of syncytial layer of cells with some cytotrophoblasts present. *B*, Dark granules which show red in color and indicate presence of glycogen storage. This storage does not occur in the normal term villi. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)

Fig. 11.—Placenta from patient with recurrent prematurity. Best carmine glycogen stain. *A*, Chorionic villi are degenerated; syncytial layer has disappeared. *B*, Large cytotrophoblast cells are found in large numbers; nuclei are hyperchromatic. *C*, Dark-staining granules indicate large deposition of glycogen. Note lack of vascularity. Chorionic gonadotrophin excretion levels increased as pregnancy continued while pregnandiol excretion levels decreased. ( $\times 600$ ; reduced  $\frac{1}{2}$ .)

Fig. 12.—Placenta from patient with severe pre-eclampsia. Modified Masson stain for alkaline phosphatase. Note areas of villi degeneration. *A*, Large villus; syncytial layer has disappeared. *B*, Note large numbers of cytotrophoblast cells. Chorionic gonadotrophin levels markedly elevated. ( $\times 170$ ; reduced  $\frac{1}{2}$ .)



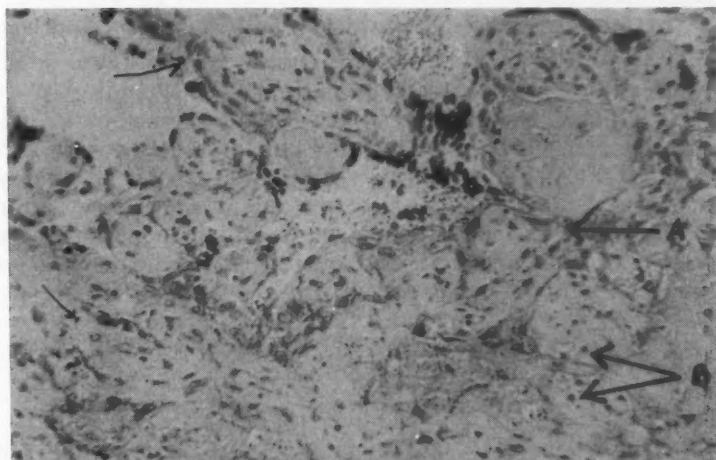


Fig. 10.



Fig. 11.

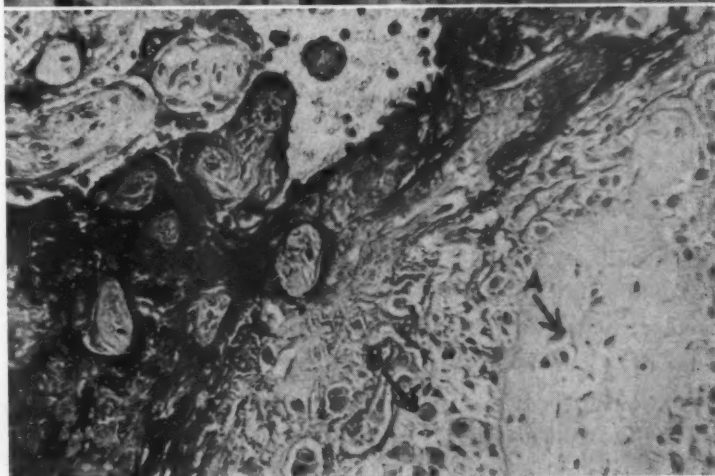


Fig. 12.

Figs. 10-12.—For legends see opposite page.



diabetes, isoimmunization, and toxemia of pregnancy, as well as in some cases of premature birth. This rise seemed to result from the increased activity in the cytotrophoblast of the placenta.

The rise in gonadotrophin may be taken as a warning of fetal anoxia because it has been noted that when the excretion of this substance has reached high levels, fetal death ensued. In some cases of recurrent premature birth, the output of chorionic gonadotrophin was found to be below normal in early gestation. In these cases, the peak excretion was reached later than the fiftieth day of gestation and the amount of chorionic gonadotrophin remained constantly high. The continuous high output of this hormone with failure to recede to normal levels preceded premature labor and birth in some patients.

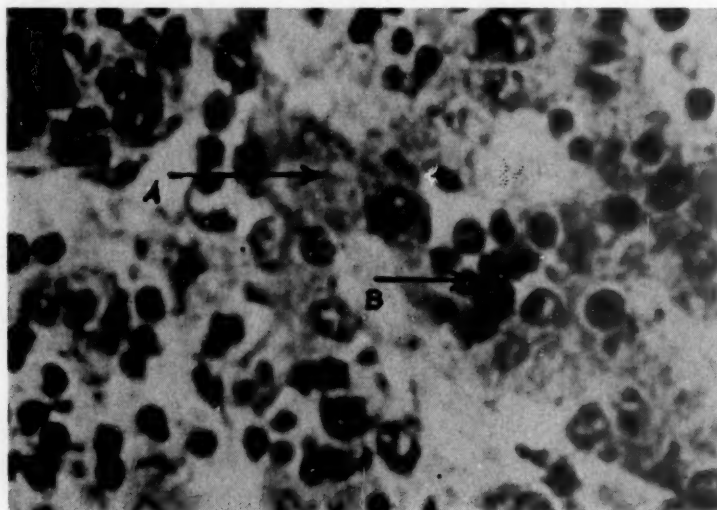


Fig. 13.—Liver from fetus of patient with toxemia of pregnancy. Term pregnancy. Best carmine stain. A, Few liver cells, no glycogen present. B, Large numbers of erythrocytes denoting considerable extramedullary hemopoiesis. ( $\times 360$ ; reduced  $\frac{1}{5}$ .)

The corpus luteum under the stimulation of chorionic gonadotrophin secretes progesterone until the mid-portion of pregnancy and until the original cytotrophoblast disappears from the chorion. The placenta takes over the production of progesterone from this point. It has been noted that when chorionic gonadotrophin levels increase with advancing pregnancy, urinary pregnandiol decreases. The altered excretion of these two substances may be indicative of placental degeneration (Figs. 14 and 15).

### Summary

The cytotrophoblast in the early portion of gestation can be shown, by histochemical means, not only to store glucose as glycogen in large quantities, but to produce the glycoprotein, chorionic gonadotrophin. The fetal liver during this time is involved in the beginning of hemopoiesis.

During the latter half of normal pregnancy, the site of glycogenesis is reversed, for the chorion ordinarily does not have much glucose storage while the fetal liver is active in carrying on this process.

Histochemical and histological changes which have been found to occur in the placenta in abnormal pregnancy suggest that the chorion reverts back to an

earlier type when complications are present. In this situation the liver also reverts to its earlier function of erythropoiesis and is less concerned in the storage of glycogen.

A rising titer of chorionic gonadotrophin in the urine may be a bad omen in respect to the function of the placenta. This may be particularly

Fig. 14.

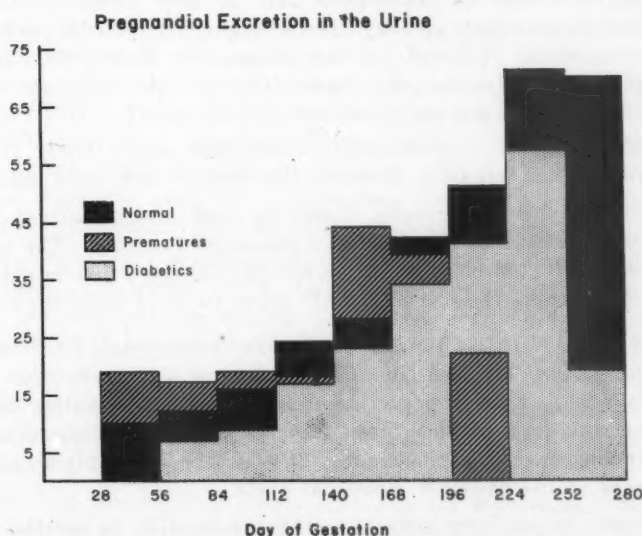
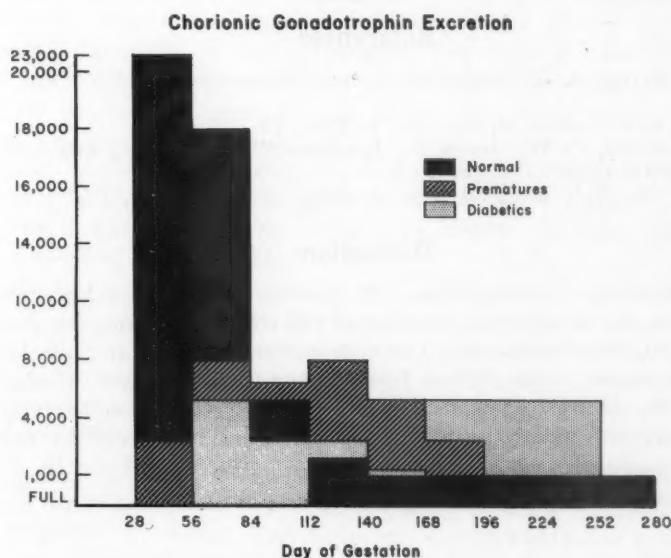


Fig. 15.

Fig. 14.—Excretion of chorionic gonadotrophin in normal and abnormal patients. Note that the premature group maintained greater excretion than is normal with the amount never decreasing to normal levels. Cytotrophoblasts remained in the placenta to account for this increased excretion. Excretion of chorionic gonadotrophin in diabetes increased significantly as pregnancy advanced.

Fig. 15.—The excretion of pregnandiol in normal and abnormal patients. Note the marked drop in excretion in the premature group after the one hundred ninety-sixth day of gestation. Excretion of pregnandiol in the diabetes group was always below normal, significantly after the two hundred twenty-fourth day of gestation.

true in cases of isoimmunization where it is difficult to evaluate the pregnancy by the antibody titers.

I wish to acknowledge the assistance of Dr. Tyree Wyatt, Professor of Pediatrics, State University of New York Upstate Medical Center, for his assistance in reviewing histology sections of the fetal livers; Miss Lillian Purdy, of the Department of Pathology, for the histological stains, and Miss Stella Zimmer and Mr. Lou Georgianna from the Department of Photography.

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### Discussion

DR. C. H. MAUZY, Winston-Salem, N. C.—The author's cytologic observation on the phasic variation in the glycogen content of the chorion confirms the earlier biochemical study of Villee, showing a large glycogen content of the early placenta with progressive decreases toward term. Villee further showed that oxygen uptake, lactate and pyruvate production, as well as glucose production, decreased progressively throughout pregnancy. The placenta thus appears to age metabolically as well as morphologically.

The present study also is consistent with the observations of McKay, Hertig, and associates, who showed comparable changes in glycogen and phosphatase content of placentas.

The particularly interesting aspect of Dr. Hughes' study is the inverse relation between the glycogen content of the chorion and the fetal liver. To what extent these are causally related is uncertain although the changes observed in pathologic pregnancy suggest that the variations observed are not incidentally associated. However, because of the extreme lability of glycogen, one would like to know how soon after death were sections of the liver made and was the tissue immediately fixed?

Further study, perhaps by radioisotope techniques, may clarify the particulars of carbohydrate turnover and transfer between the chorion and fetal glucose stores.

This type of study is particularly timely in view of the current interest in fetal wastage that may be related to the failure of placental function. The suggestion by the author that a rising titer of chorionic gonadotropin in the urine might be a bad omen in respect to the function of the placenta could prove to be of definite clinical significance.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—In recent years, Dr. Hughes has reported studies which have certainly clarified our understanding of the possibilities when our patient aborts in the early weeks of pregnancy. The recommendations regarding treatment made by Hughes and associates at that time were based upon the histochemical evidences they had noted of certain nutritional deficiencies within the endometrial glands during the post-ovulatory phase of the patient's menstrual cycle.

Since that time, in our own biopsies we have been able to see the evidences of the deficiencies described. We are convinced that spontaneous abortion is not as likely to recur in women with such a deficiency in their biopsies, if they do not again conceive until preconceptional biopsy does reveal an endometrium adequately prepared for the nutritional needs of an embedding conceptus.

It is interesting, somewhat unique, and in a sense gratifying to see the same investigators report confirmation of earlier studies plus observations increasing the significance of their earlier reports. Today we have learned of evidence detected by the

same histochemical techniques, that the placenta may show changes which are associated with dysfunction of the fetal liver. These observations, they advise us, do not as yet warrant attempts to conclude whether in such cases placental inadequacies have resulted in damaged fetal parenchyma or whether the placental changes noted indicate fetal pathology for which a relatively embryonic placenta is trying to compensate. The findings reported do lend support to several seemingly well-established observations. Metabolic activities characteristic of the early placenta are normally not continued into the last half of pregnancy. When the placenta shows evidence of the persistence of these earlier functions into late pregnancy usually all is not well with the fetus. Persistence or the reappearance of cells in considerable number has been noted repeatedly by the pathologists describing the placenta in cases of fetal death associated with erythroblastosis, maternal diabetes, and toxemia.

Certainly we are all anxious to learn of ways by which fetal injury can be detected before fetal damage beyond repair has occurred. Certainly we have learned that the antibody titers do not provide us with a reliable means of determining when termination of pregnancy is advisable in suspected erythroblastosis. I would like to ask Dr. Hughes if he believes it likely that many of us could employ chorionic gonadotropin levels to warn us of impending fetal damage.

Is it not true that a single assay of gonadotropins in maternal urine taken when fetal difficulty is suspected would be of no value unless such assays had been done routinely in the earlier weeks of pregnancy and the results were available for comparison with the later figures? Should we not express the hope that continued investigation will eventually produce a method of determining changes in placental function and capacity more widely available and perhaps more practical than assays of gonadotropins in maternal urine, and a bit more timely than can be provided by the postdelivery or post-mortem histology of the placenta?

DR. ERNEST W. PAGE, San Francisco.—Dr. Hughes has presented data relative to the urinary excretion of chorionic gonadotrophin and pregnanediol during pregnancy, the amount of glycogen in the placental membrane and the fetal liver, the presence or absence of phosphatases in these tissues, and some anatomic observations. The fact that these data are presented in one paper implies that there is some relationship between all of these things, but this is not necessarily so. The chorionic gonadotrophin output is probably a reflection of the number of functioning cytotrophoblast cells. Its increase in late pregnancy may reflect placental damage because only the cytotrophoblast has the power of reproducing itself in response to injury. On the other hand, when syncytium is destroyed, its apparent inability to reproduce itself may account for the decline in estriol and pregnanediol excretion in such conditions as pre-eclampsia.

These hormonal events are probably unrelated to the alkaline phosphatases (whose functions are really not known) or to the glycogen problem. Glycogen deposition may be related, as Wislocki pointed out, to the degree of oxygenation of the cells at the time of removal from the body and fixation.

In any event, the presence or absence of glycogen in the placental membrane has little to do with glucose transfer from mother to fetus. Glucose is actively transferred from the maternal plasma (not from the decidua) to the fetal plasma. This takes place with great rapidity and does not involve glycogen formation.

The ability of the early placenta and the corresponding inability of the early fetal liver to synthesize glucose was well demonstrated by Villee, as mentioned by Dr. Mauzy. He worked with tissue slices and demonstrated the synthesis biochemically. I doubt that one could have established such facts by morphologic or histochemical criteria alone.

Working with isolated, perfused human placenta, we have found that the intracellular penetration of glucose depends initially upon the presence of insulin. We have no evidence, however, that the rate of glucose utilization—which is about 1 Gm. per hour per kilogram—is altered by insulin.



Dr. Hughes is touching on the periphery of some very important problems but, to get to the core, I fear that he must use in vitro biochemical approaches to the intermediary metabolism of carbohydrates, the function of phosphatase, the significance of glycogen deposition, or the role (if any) which chorionic gonadotrophin and progesterone have in these diverse problems.

DR. HUGHES (Closing).—In respect to the fixation of the tissue, we have placed tissue in the solution, as soon as possible, many times within the hour, and many times in less than the hour. However, we have purposefully left some tissue in the refrigerator at a constant cold temperature, and we find that glycogen from the liver disappears rather slowly. Also, we have cardiac muscle and diaphragm muscle as a control but glycogen does not disappear as quickly from these structures as it does from the fetal liver. In any histochemical method, you must fix the tissue almost immediately.

When the chorionic gonadotrophin titer has been noted to rise by any significant amount in a case with isoimmunization, the life of the fetus has been more in jeopardy. We have had 8 or 10 cases where the chorionic gonadotrophin level has remained slightly elevated and all babies have had to have exchange transfusions but they have lived. Whenever the babies have died, the titers have gone up appreciably.

I agree with Dr. Page. We do not feel that histochemical methods are the direct ways of determining these metabolic processes. They merely give us a guide.



## *Obstetrics*

### **IDIOPATHIC THROMBOCYTOPENIC PURPURA IN PREGNANCY**

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**I**DIOPATHIC thrombocytopenic purpura in pregnancy is rare. Peterson and Larson<sup>1</sup> in 1954 reviewed the literature and found reports of only 65 pregnancies in 47 mothers with idiopathic thrombocytopenic purpura. Many other types of purpura were excluded from their study. Although other types are more common, Saltzman<sup>2</sup> found only 80 cases of purpura of all types during pregnancy reported in 1948.

Thrombocytopenic purpura can be idiopathic or secondary to other diseases, such as leukemia, infection, toxic poisoning, excess radiation, etc. (Wintrobe's<sup>3</sup> classification). The idiopathic type can usually be easily differentiated from the secondary type. The idiopathic type has a normal or increased number of megakaryocytes in the bone marrow. The secondary type has a decrease or absence of megakaryocytes and the history and findings of associated disease.

The idiopathic type is divided into acute and chronic varieties, the differentiation of which is well outlined by Dameshek.<sup>4</sup>

The following case, we believe, is one of acute idiopathic thrombocytopenic purpura, occurring during the eighth month of pregnancy.

#### **Case Report**

The patient was a 17-year-old white girl, gravida i, para 0, who had had no abortions and whose last menstrual period was on July 16, 1957. The expected date of confinement was April 23, 1958. She entered the hospital on March 16, 1958, with the complaints of bleeding from the nose and gums, starting 2 days prior to admission, and a bright red

color to the urine beginning on the day of admission. The prenatal course had been normal except for an episode of acute pyelitis occurring in the first trimester, which was treated with Gantrisin, Furadantin, and streptomycin. She had been on the following medications during the prenatal course: Mol-Iron, calcium, vitamins, Neo-Synephrine nose drops, and had received two poliomyelitis vaccine injections, the last having been given the week prior to admission. She had also been given vitamin C and Diamox the day of the onset of the epistaxis and bleeding gums. Super-anahist had been taken about one month previously because of cold symptoms. Prior to the present situation, the patient had no history of bleeding difficulties, blood dyscrasias or hypersplenism. Her prenatal weight gain had been 22 pounds and the prenatal blood pressure readings had been in the range of 110/60. There was no more than a trace of edema and no albuminuria. The urine had been negative since treatment for pyelitis in the first trimester. The family history disclosed no evidence of bleeding tendencies.

*Physical Examination.*—On admission, examination revealed a well-developed white girl with the uterus enlarged to the size of a 35 weeks' gestation. There was slight bleeding from the nasal mucosa and from the gums. Purpuric lesions were present in the mucosa of the mouth, nose, and vagina. Several small conjunctival hemorrhages were present. There were purpuric lesions scattered over the patient's entire body but they were most prevalent over both lower legs. Several small cervical nodes and a small right axillary node were palpable. The muscles were generally tender and the pressure of a blood pressure cuff was quite painful. The general condition of the patient, including blood pressure and pulse, was normal. Fetal heart tones were good and there was no evidence of adverse effect upon the pregnancy. The spleen and liver were not palpable. There was no evidence of the onset of labor. The tourniquet test was strongly positive.

*Laboratory Data.*—In the prenatal clinic the patient's white count was 10,650 with 76 neutrophils, 23 lymphocytes, and 1 eosinophil. The hemoglobin was 12.5 Gm., erythrocyte count 3.54 million, and the blood type was O, Rh positive. A photofluorogram of the chest was normal. Urinalyses since the clearing of the pyelitis in September, 1957, had been negative for albumin and pus.

With the present admission, the urine was grossly bloody. The white count was 11,700 with 67 per cent neutrophils, 7 band forms, and 3 juvenile cells. The coagulation time was 9 minutes. No platelets could be found on the blood smear. The hemoglobin was 10.7 Gm. Bleeding time was 25 minutes. Clot retraction after 12 hours was not present. The prothrombin time was 100 per cent. The fibrinogen level was 341 mg. per cent. The electrocardiogram was normal. Bone marrow studies showed atypical megakaryocytic hyperplasia consistent with thrombocytopenic purpura. There was a slight generalized hyperplasia of the bone marrow but it was almost devoid of platelets.

The laboratory data during the acute phase of the disease is given in Table I.

TABLE I

DATE	BLEEDING TIME	COAGULATION TIME	PLATELETS	CLOT RETRACTION	TOURNIQUET TEST	FIBRINOGEN
3/16/58	25 minutes	9 minutes	None seen		+	
3/17/58			None seen	12 hours		
3/18/58	3 minutes	6½ minutes	8,040			
3/19/58			7,060		+	341 mg. %
3/20/58			7,960			
3/21/58	2½ minutes		48,620			
3/22/58	2½ minutes		62,400			
3/23/58			225,600			
3/25/58			253,230			
3/26/58			212,800	1-4 hours		

*Hospital Course.*—The patient was placed on bed rest, given a low-salt diet and prednisone, 10 mg. every 6 hours. She was also given vitamin C, 300 mg. daily and

vitamin K, 15 mg. daily. A transfusion of 500 c.c. of fresh whole blood was given immediately after admission. The platelet count was between 7,000 and 8,000 per cubic millimeter for the first 4 days after admission. On the fifth day it rose to 46,000 and on the sixth day it was over 200,000 and remained at this level throughout the hospital stay. The patient was afebrile during the entire hospital course.

On the day following admission, there was still slight oozing of blood from the nasal mucosa and the urine was still grossly bloody. On the second day after admission, the mucosal bleeding stopped and the urine was less bloody. By the third day the urine was completely clear of gross blood. A tourniquet test was only questionably positive and there was no tenderness of the tissues when the tourniquet was applied as there had been initially. She was continued on prednisone, 10 mg. every 6 hours, and a week following admission was given 40 units of ACTH. No further bleeding occurred after the third hospital day and the platelet count remained normal after the sixth hospital day. The bleeding time on the fifth hospital day was  $2\frac{1}{2}$  minutes.

*Interval Course.*—At the time of discharge, 12 days after admission, the clot retraction was normal, bleeding time was normal, the platelet count was normal, and the patient was discharged on 15 mg. of prednisone daily plus 80 units of ACTH weekly.

On March 29, 1958, the day following discharge, she was admitted in early labor and physical examination at that time showed no evidence of purpura. The platelet count was 218,000; the hemoglobin was 13.2 Gm.; the red cell count was 4.2 million.

*Hospital Course.*—After a normal  $6\frac{1}{2}$  hour labor, the patient was delivered of a 5 pound, 13 ounce female infant with the aid of low forceps under spinal anesthesia. A right mediolateral episiotomy was performed. The patient tolerated the labor and delivery well. There was no excessive bleeding from the episiotomy or the uterus following delivery. During this hospital stay the mother was given prednisone, 20 mg. daily. She remained afebrile throughout the puerperal period, and the platelet count, bleeding and clotting time remained within normal limits. The baby showed no evidence of purpura or laboratory findings of thrombocytopenia. The baby was breast fed, progressed well, and both mother and infant were discharged on the sixth postpartum day. Close follow-up since that time for the past 4 months has shown the platelet count, tourniquet test, and clot retraction to be within normal limits and the patient has had no recurrence of purpura.

### Comment

The pathogenesis of idiopathic thrombocytopenic purpura is discussed in many articles and standard hematology texts,<sup>1, 3-6</sup> and will not be considered here except to emphasize that I.T.P. is a disease of two distinct factors—decreased platelets and increased capillary fragility. Decreased platelets may be due to deficient platelet formation in the bone marrow and increased destruction by platelet antibodies. The spleen is believed to play a part in the production of a humoral substance which prevents formation of platelets in the bone marrow. Capillary fragility is responsible for the purpuric manifestations of this disease. The capillaries in I.T.P. have been found to be abnormal.<sup>7</sup> The vascular factor is partially reversed by ACTH and cortisone.

Increased capillary fragility is shown by the tourniquet test, and increased bleeding time, delayed or poor clot retraction, decreased platelets, and normal clotting time, prothrombin time, and fibrinogen levels are all characteristic.<sup>3</sup>

In the management of the disease, it should be remembered that the acute type is usually self-limited. It responds to ACTH and cortisone along with supportive measures, platelet transfusions, and blood replacement by fresh blood collected in silicon-treated containers.<sup>4</sup> With these measures the acute case will usually subside rapidly and if there is no recurrence after 4 months



it can be assumed that it is not chronic; the latter in many cases may necessitate splenectomy. In general, the treatment of idiopathic thrombocytopenic purpura during pregnancy is the same as when pregnancy is not present.<sup>8</sup> There is always risk, however, of massive bleeding from mucous membranes, bleeding into a "vital area," cerebral hemorrhage, and bleeding from episiotomy or cesarean section incision if delivery occurs or is necessitated during the acute episode. Bleeding from the postpartum uterus is not excessive, however, since control of bleeding from the placental site is due to mechanical action of the uterine muscles.

It has been shown that splenectomy can be safely performed during pregnancy in the chronic cases,<sup>1,9</sup> although the fetal mortality rate is then increased to 30 per cent. The maternal mortality rate is generally low (2 to 3 per cent).<sup>1</sup>

The newborn may show evidence of the disease (50 to 75 per cent) clinically or by laboratory tests, especially if the mother's platelet count is low at the time of delivery.<sup>1</sup> But the disease in infants is usually self-limited and signs and laboratory findings disappear in about 2 months.

### Summary

A case of acute idiopathic thrombocytopenic purpura during pregnancy is presented. A discussion of the classification and differentiation of types of thrombocytopenic purpura is given and the salient points in pathogenesis, laboratory findings, treatment, and complications are mentioned.

*Addendum.*—At the time of publication the patient is again pregnant and shows no evidence of recurrence of thrombocytopenic purpura.

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## FATAL CORONARY ARTERY DISEASE DURING THE EARLY POSTPARTUM PERIOD

### Report of One Case

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CORONARY artery disease among women of childbearing age is rare, and it is even less frequent during pregnancy or the puerperium. Mendelson<sup>1</sup> reviewed the literature and collected 21 cases, adding 4 cases of his own. In 1955, Siegler<sup>2</sup> reported one case of myocardial infarction complicating pregnancy. There are no reports in the literature, as far as we know, of coronary occlusion during the early postpartum period, with the exception of an undocumented case mentioned by Kolisko.<sup>3</sup> Because we recently encountered fatal coronary artery disease in a 21-year-old patient on the fourth postpartum day, we wish to add this case to the medical literature.

N. B., a 21-year-old Negro woman, gravida<sup>ii</sup>, para 0, was admitted to the City Hospital of Cleveland on Oct. 24, 1956. She was at approximately the fortieth week of gestation and was delivered of a macerated stillborn baby per vaginam 15 hours after admittance. On the fourth postpartum day, she died suddenly. The family history was noncontributory. There was no history of hypertension, nephritis, thyroid disease, allergy, or venereal disease. She had had one spontaneous abortion at approximately 5 months' gestation and in 1952 had had an appendectomy. Her blood type was O Rh positive. She had visited the clinic six times, and the course of the present pregnancy had been uneventful. She had been normotensive (120/65) at all visits. Urinalysis was negative. The hemoglobin was 12.0 Gm. and the hematocrit 40 per cent. Her usual body weight was 130 pounds and the total weight gain during this pregnancy was 18 pounds. Her height was 5 feet, 4½ inches. On no occasion was peripheral edema demonstrated. She had no complaints except at the last visit. At that time she complained of a slight cough and dizziness, but her chest was clear, no moist râles or heart murmurs were heard. There was no history of nocturnal dyspnea, hemoptysis, or chest pain.

She came to the hospital in active labor on Oct. 24, 1956. The fundus measured 26.5 cm., and the fetus was in vertex presentation. The cervix admitted one finger and the presenting part was at the level of the spines. Fetal heart sounds were recorded as 136 per minute over the left lower quadrant on admission, but 3 hours later no fetal heartbeat could be heard. The membranes had ruptured before admission. After approximately 15 hours of labor, under local pudendal anesthesia, a term macerated stillborn baby girl, weighing 5 pounds, 9 ounces, was delivered with low forceps from the left occipitoanterior position. The patient's immediate postpartum condition was good. The blood pressure was 120/60. No excessive vaginal bleeding or other complications were noted. Approximately 8 hours after delivery, the patient's temperature rose to 38.8° C., the pulse was 100 per minute, and the respiratory rate was 22 per minute. On the first day post partum, she vomited a small

amount of greenish material which contained no blood. She complained of a sore throat, and on examination the pharynx was found to be congested. Intramuscular penicillin and streptomycin were started. Intravenous fluids consisting of 5 per cent glucose in water were given. On the second day postpartum, she was still vomiting a small amount of similar material. Her temperature was 39.0° C. The heart and lungs were clinically entirely normal. The abdomen was moderately distended and bowel sounds were hypoactive. With the patient in an upright position, an x-ray film of the abdomen showed dilated loops of small bowel, with fluid levels. Involution of the uterus was normal. The fundus of the uterus was 3 fingerbreadths below the umbilicus, and there was good drainage of lochia which

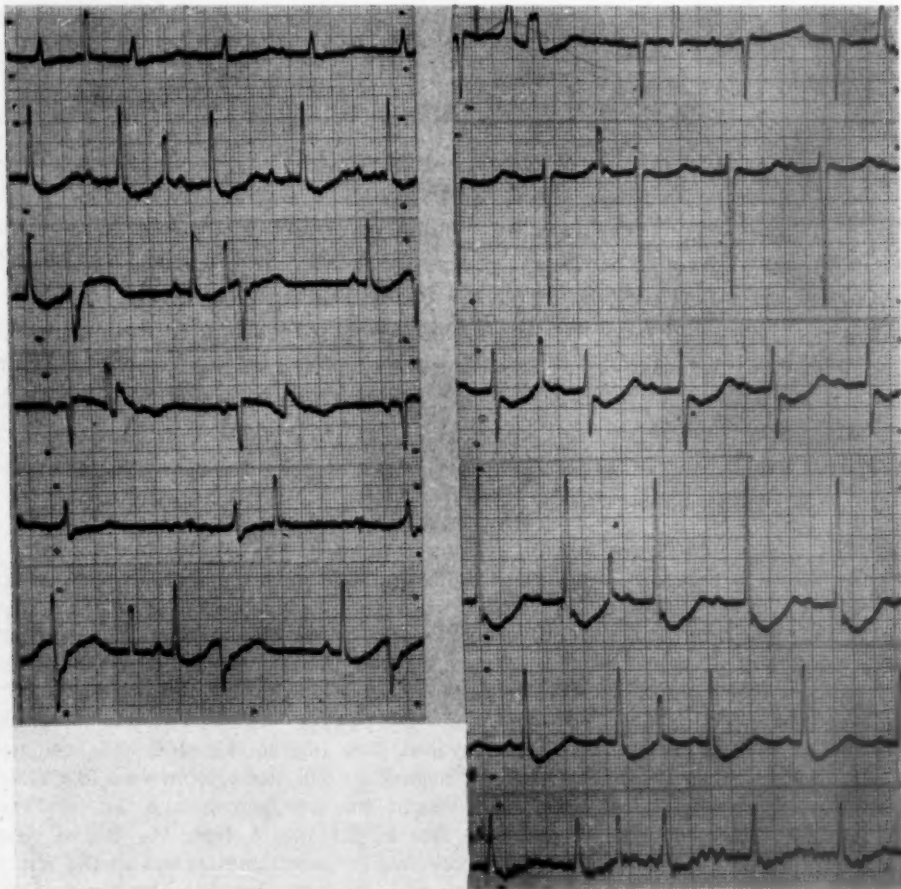


Fig. 1.—ECG (taken on Nov. 29, 1956) showing a sinus arrhythmia, rate 68 per minute, frequent bigeminal ventricular beats and a transient first-degree atrioventricular block, with the P-R interval changing from 0.16 to 0.32 second. The Q-T or Q-U interval measured 0.62 second. The S-T segment was markedly depressed and upwardly concave in all the standard and unipolar limb leads, except  $aV_2$ , and in the precordial leads from  $V_2$  to  $V_6$ . In a  $V_2$  the S-T segment was elevated and upwardly convex. The T wave (or U wave) was terminally upright in all leads in which the S-T segment was depressed. The record was considered to be consistent with hypokalemia.

was not foul. There was no evidence of thrombophlebitis of the lower extremities. Intravenous 5 per cent glucose in water with Terramycin was started in an effort to treat possible pelvic peritonitis. The white blood count was 12,000 with 68 per cent polymorphonuclear cells. On the third day post partum, the patient was afebrile except for one occasion when the temperature was 38.0° C. Her general condition was improved. The pulse rate slowed to 90 per minute. The abdomen was less distended, and the bowel sounds were definitely normal. The patient was passing flatus. There was good drainage of lochia and normal uterine involution. The daily urinary output was approximately 4,000 c.c.

Blood chemistry studies showed the following: sodium 142 mEq. per liter, chloride 105.3 mEq. per liter, and potassium 1.9 mEq. per liter. Neurological examination was within normal limits and clinically, the patient did not appear to be in severe hypokalemia. An electrocardiogram was ordered. On the fourth day post partum, the patient's general condition was much improved. She felt perfectly well and was afebrile. The report of the previous day's electrocardiogram showed transient first-degree A-V block consistent with hypokalemia (Fig. 1). Before intravenous 5 per cent glucose in water and 5 per cent glucose in saline with 120 mEq. potassium chloride were started, she was allowed to be up and about in the room for the first time in the postpartum period. She was very happy and walked around for about 5 minutes without assistance. She then went back to bed without any evidence of stress. She did not complain of anything at all. Three minutes later she suddenly collapsed, and the blood pressure could not be obtained. She died within 2 or 3 minutes. No cyanosis or convulsions were noticed.

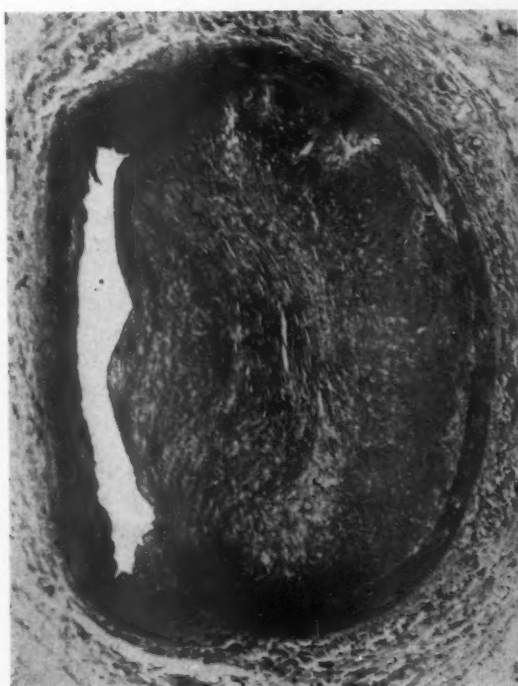


Fig. 2.

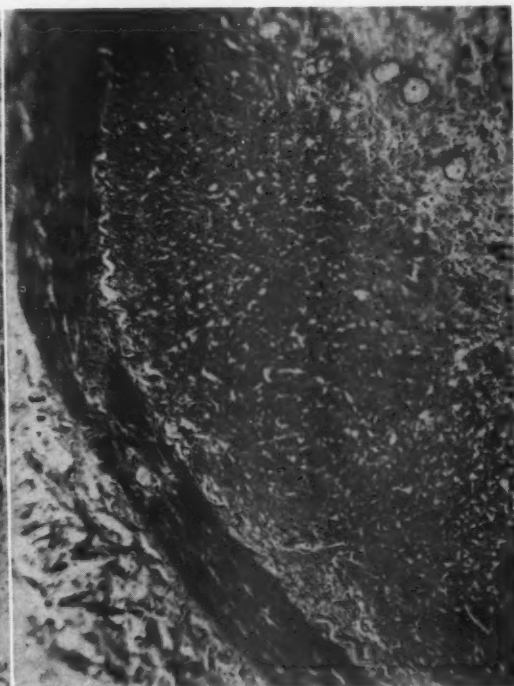


Fig. 3.

Fig. 2.—Left anterior descending coronary artery. Note almost complete obliteration of the lumen of the artery. The thickness of the intima appears normal on the right side, while enormous proliferation of the intima is seen on the left side of the lumen. The differential staining ruled out a recent blood clot. ( $\times 15$ ; reduced  $\frac{1}{6}$ .)

Fig. 3.—Section of Fig. 2. Under high magnification the intima shows a marked proliferation, prominent fibrosis, new vessel formation and atherosclerosis. ( $\times 125$ ; reduced  $\frac{1}{6}$ .)

Immediate postmortem urinalysis, hemogram, and electrolytes were all within normal ranges except for potassium. The serum potassium was 2.1 mEq. per liter. The tentative clinical diagnosis was "deep pelvic thrombosis with sudden massive pulmonary embolism."

**Autopsy Findings.**—*Central Nervous System:* Focal subarachnoid hemorrhages in the parietal lobe. *Cardiovascular System:* Recent subendocardial infarct in the left ventricle and interventricular septum. Coronary arteriosclerosis with marked stenosis of the anterior descending branch of the left coronary artery. Moderate arteriosclerosis of the aorta. *Respiratory System:* Bilateral pulmonary edema. Chronic passive hyperemia of lungs. Focal fibrosis with caseation consistent with tuberculosis of left lower lobe. Fibrotic pleural adhesions. *Digestive System:* Chronic passive hyperemia of liver. Foci of chronic granulomatous inflammation, consistent with disseminated tuberculosis in the liver. Surgical absence



of the appendix. External hemorrhoids with organizing thrombi. *Urogenital System:* Bilateral hydronephrosis. Bilateral hydroureter. Chronic cystitis with submucosal hemorrhage. Diverticula of the bladder (symmetrical and bilateral). Recently gravid uterus with involution. *Lymphoid and Hemopoietic System:* Chronic granulomatous inflammation with fibrosis and caseation, consistent with tuberculosis in the bronchopulmonary lymph nodes. *Endocrine System:* No pathological diagnosis. *Skeletal and Muscular:* No pathological diagnosis.

*Pathological Diagnosis.*—Arteriosclerosis with marked stenosis of the descending branch of the left coronary artery (Figs. 2 and 3). Recent subendocardial infarction of the left ventricle and interventricular septum.

### Comment

The death rate from coronary artery disease among women is estimated by Dublin as quoted by Mendelson<sup>1</sup> to be 3.5 per 100,000 during the ages from 35 to 44 years as compared to 16 per 100,000 for the same age group in males. The total number of cases of coronary artery disease related to pregnancy which have been reported in the literature is 26, and the total number of deaths among these is 7, or 26.9 per cent. The latter figure includes Kolisko's<sup>3</sup> patient who died one month post partum with no record of the details of the cause of the disease.

The first well-documented case of coronary occlusion during pregnancy was recorded in 1935 by Reiss and Frankenthal.<sup>4</sup> The clinical diagnosis was supplemented by the electrocardiogram. Since then 9 clinically well-documented cases of coronary artery disease during pregnancy have been reported. Of the total of 10 cases in which the diagnosis of coronary occlusion during pregnancy was made by electrocardiogram, 4 cases occurred in the first trimester, 3 in the second trimester, and 3 in the last trimester of pregnancy. Only one case in the latter group was fatal, and no autopsy was performed. Only 5 fatal cases of coronary artery disease during either the prenatal course, delivery, or the puerperium have been reported in the literature. One was documented by electrocardiogram, and the remaining 4 occurred prior to the use of the electrocardiogram. The diagnosis was made clinically and in only one case was the diagnosis confirmed by autopsy.<sup>5</sup>

Our case, which is proved by autopsy findings, appears to be the first documented report in the literature of coronary occlusion during the early puerperium.

The diagnosis of coronary insufficiency in this case was not made prior to death, because there were no history, symptoms, or signs of the condition. The negative autopsy findings in the peritoneal cavity and viscera did not explain the intestinal symptoms and the clinical or radiological evidence of paralytic ileus and peritoneal irritation. In the presence of the radiological findings, however, the abdominal symptoms cannot be attributed to the coronary artery disease. Despite the negative pathological, anatomical, and bacteriological findings of infection, the rise in temperature in the immediate postpartum period in our patient with the history of fetal death in utero was indicative of an infection, and the rising hemoglobin level with the initial value of 12.0 Gm. is suggestive of dehydration even in the absence of its clinical evidence. The early therapy with antibiotics and hydration with intravenous glucose and water did not permit the development of the full picture of the infectious process. These measures, however, failed to prevent the paralytic ileus and hypokalemia. The patient had been followed during the entire prenatal course and no clinical signs of hypokalemia had been noted.

It is likely that hypokalemia developed on the first postpartum day subsequent to labor and delivery in the presence of infection and contributed to the

development of paralytic ileus. The hypokalemia was aggravated by the additional loss of potassium into the bowel. Furthermore, the excessive utilization of the available extracellular potassium was probably maintained by the intravenous glucose administration. We do not know whether the adrenal corticoids, which might have been elevated during the stress of labor, death of the fetus in utero, delivery, and the febrile condition, added to the hypokalemia. In view of the normal value of the other serum electrolytes, it is not likely. Furthermore, the placenta as the source of the sodium-retaining steroids had been removed, and the serum potassium, which might have been low during labor or immediately thereafter, would be expected to increase during the postpartum period in a patient with healthy kidneys and adrenals.

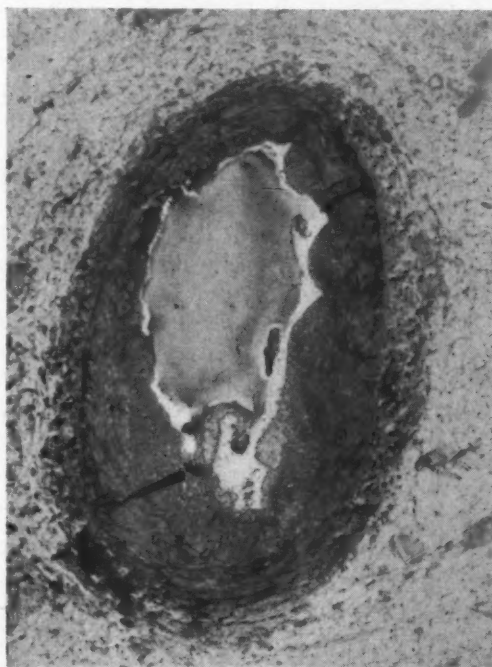


Fig. 4.—The right descending coronary artery. A smaller degree of proliferation of the intima, similar to that in the left descending coronary artery.

The hypokalemia reached its peak on the third postpartum day (serum potassium 1.9 mEq. per liter) and kaliemia had begun to increase thereafter, as is evident from the increase in potassium to 2.1 mEq. per liter, the disappearance of the paralytic ileus, and general improvement of the patient.

In view of the histological findings of almost complete obliteration of the lumen of the coronary arteries and in view of the lack of clinical signs of critical hypopotassemia, we cannot attribute the death of the patient to hypokalemia, although it is evident from the electrocardiogram that the hypokalemia was significant to cause a change in the cardiac tracings. Potassium has been recognized as essential for normal function of the myocardium. McAllen<sup>6</sup> described widespread myocardial fibrosis and focal necrosis of the myocardium in 2 cases of prolonged and severe potassium deficiency. In our case, we do not have enough evidence to postulate that hypokalemia had devitalized the syncytial myofibrils, the cells of the vessel wall, and thus enhanced the myocardial infarction. After assessment of the pathological anatomical findings, the course of the disease, and the changes in the electrocardiogram, it is suggestive, however, that the hypokalemia aggravated the coronary artery disease

and contributed to the fatal outcome at this time. It is evident from the histological findings that even if the patient had survived the pregnancy, delivery, and puerperium her life expectancy was minimal.

The values of the serum cholesterol in this patient had not been obtained, and the histological studies cannot rule out the presence of hypercholesterolemia as an etiological factor in the coronary artery disease in this young patient.

We have been unable to establish any possible evidence of long-standing hypokalemia in our patient and no evidence of this being a familial disease could be obtained since the patient had only foster parents and no blood relatives have been found.

Infection as the etiological factor in coronary artery disease cannot well be postulated in view of the absence of polymorphonuclear infiltration into the vessel wall and the failure to find the bacteriological agents in serial sections of the coronary vessels.

Degenerative changes of the media and proliferative changes of the intima resulting in the almost complete obliteration of the lumen of the left (Figs. 2 and 3), and partial obliteration of the right coronary artery (Fig. 4) are unusual findings in a 21-year-old woman and during pregnancy. It is known that the degenerative vascular changes cannot always be attributed to the aging processes. Arteriosclerotic aortas without evidence of senescence have been found in young men in their twenties.<sup>7</sup> No reports of similar findings among women of this age are known and in view of the modern aspects of the relationship of sex hormones and arteriosclerosis, the vascular changes would be expected to be ameliorated by pregnancy. The diversified effect of hormones on the cardiovascular tissue has been recently revived by the work of Wuest, Dry, and Edwards,<sup>8</sup> and further evidence of the anabolic effect of estrogen and antianabolic or catabolic effect of the adrenal corticoids and progesterone on this system has been obtained. Griffith<sup>9</sup> observed the increased frequency of coronary atherosclerosis in bilaterally oophorectomized women.

It is conjectural whether or not the excessive proliferation of the intima of the coronary arteries with moderate degenerative changes in the remaining layers of the arteries can be attributed to the altered ratio of estrogen and progesterone and linked with the death of the fetus in utero. This problem remains to be solved by future investigation of the hormone action on the cardiovascular system.

### Summary

A case of coronary occlusion in a 21-year-old patient on the fourth postpartum day is reported. The associated hypokalemia is considered as a possible aggravating factor in the fatal outcome of the disease during the early puerperium.

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## DEPARTMENT OF CURRENT OPINION

### *Pertinent Comments*

#### LUNAR PERIODICITY IN HUMAN REPRODUCTION: A LIKELY UNIT OF BIOLOGICAL TIME

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THE moon has been surrounded with romantic significance in song and story through the ages. The menstrual cycle, by its very name, implies a relation to the moon or the month, which is based originally on the cycle of the moon's phases. Textbooks in the biological and medical sciences state that a lunar month is 28 days in length, that the average menstrual cycle is 4 weeks or 28 days, and that human gestation averages "10 lunar months or 280 days" from the onset of the last menstrual period and 266 days or  $9\frac{1}{2}$  "lunar" months from conception.<sup>1, 2</sup> Despite the general use of this "lunar" unit, any demonstrable relation between lunar and human sexual or reproductive phenomena has been doubted or denied in a number of reports on the human menstrual cycle.<sup>3, 4</sup>

Four years ago, in 1954, upon noticing that the lunisolar Jewish calendar had only 29 and 30 day months, we suspected that there might be some inaccuracy in the teaching that a lunar month is 28 days. Reference to astronomical treatises revealed that the mean synodic lunar month (i.e., new moon to new moon) is 29.53 days. It thus appears that the 28.0 day lunar month is a fiction, which is more inaccurate for measuring time between new moons than is the average 30.4 day solar month ( $1/12$  of 365 $\frac{1}{4}$  days).

Ten synodic lunar (or sun-moon) months are 295.3 days, but 9 are 265.8 or, to the nearest whole number, 266 days, the estimated mean duration of pregnancy from conception, according to modern authorities.<sup>1</sup> A song of *The*

†Died Sept. 12, 1957.



*Passover Haggadah* also proclaims: "Nine are the months of pregnancy." Although this coincidence could be purely fortuitous, we decided we might give credence to an interrelationship between the human reproductive cycle and the synodic lunar cycle, (a) if the mean ovulatory or menstrual cycle—the postulated unit of the reproductive cycle—were  $1.00 \pm 0.01$  mean synodic lunar month, and (b) if pregnancy averaged  $9.50 \pm 0.01$  such months from the onset of the last menses, in view of the evidence that conception (fertilization) or ovulation occurs half a cycle away from the onset of menstruation. Furthermore, (c) any fluctuations in the occurrence of menstruation, ovulation, or conception in relation to the synodic lunar month would suggest some relation between these processes and the lunar cycle or at least indicate a lunar influence on these processes.

The largest published study that we found on the menstrual cycle was by Arey<sup>1</sup> who combined the results of several studies and concluded that the mean menstrual cycle in women, based on individual averages, is 29.5 days. In his opinion, "the fullest and most careful investigation yet conducted on adults" is that by Gunn and associates<sup>4</sup>; all the reliable data of Gunn's study, when properly arranged, also give a mean of 29.5 days. (Improper arrangement of data, e.g., classifying all cycles from 29.0 up to 30.0 days as 29 day cycles instead of as 29.5 day cycles, gives a final result 0.5 day below the correct mean.) Hence it appears that the mean menstrual or ovulatory cycle in women is well within our limits of  $1.00 \pm 0.01$  synodic lunar month ( $29.5 \pm 0.3$  days) rather than  $1.00 \pm 0.01$  fictitious lunar month ( $28.0 \pm 0.3$  days).

The only recent large study we found on the duration of pregnancy, conducted by workers skilled in statistical methods, was that by Gibson and McKeown,<sup>5</sup> covering over 17,000 births in Birmingham, England. According to their data, the mean duration from the onset of the last menstrual period is 280.53 or 280.54 days, rather precisely 9.500 synodic lunar months. Again the data fall well within our limits of  $9.50 \pm 0.01$  synodic lunar months.

The strongly suggestive constellation of coincidences just noted pointed to some connection or relation between these astronomical and biological phenomena. We also reasoned that since the mean duration of gestation from conception is calculated to be virtually  $9.00 \pm 0.01$  synodic lunar months, a child conceived on a given day of the lunar month would, on the average, be born 9 lunar months later on the same day of the lunar month. Thus if births are plotted in relation to the lunar month, an increase or decrease in births at any period or day of the lunar month would indicate a corresponding increase or decrease of conceptions at the same period or day of the month 9 synodic lunar cycles earlier. (Any direct lunar influence on the terminal process of parturition would be superimposed on the conception cycle.)

To ascertain the presence of fluctuations in the rate of conceptions and births during the synodic lunar month, we counted the daily live births occurring at 57 hospitals in New York City during 13 such months, beginning Jan. 1, 1954. The counting was done from lists of names of newborn infants for each day filed for each of these hospitals with the city's Health Department. All totals obtained in these arithmetical operations are solely our

responsibility. Of more than 120,000 births during these 13 lunar months, fewer births occurred on the day of the new moon than on any other day of the lunar month when the figures for the 13 cycles were totaled. The 3 day period centering on new moon day had the fewest births of any 3 consecutive days in the lunar cycle. Full moon day averaged 7 per cent more births than new moon day. But since new moon day fell on more than one legal holiday (exclusive of Sundays) in 1954, much confidence cannot be placed in the minimum of births on this day, as there are generally fewer induced or elective deliveries on holidays (and Sundays), when a certain proportion of doctors are resting from their labors.

To minimize the effect of variations arising from cultural and other factors, a study of births for 100, later extended to 112, lunar cycles was undertaken after we made an attempt to select a group of hospitals with a smaller day-of-the-week variation in birth rate than the average. By studying all hospital births in New York City for the first 12 weeks of 1955, compiled by machine by the staff of the Health Department's Bureau of Records and Statistics, we found that considerably less variation occurred in this regard at the municipal hospitals as compared with the "private" hospitals, which showed a weekend decline, most marked on Sunday. A probable explanation is that, in the private hospitals, deliveries are made to a large extent by the patient's personal physician or specialist, who is more likely to do elective deliveries on weekdays, while in the municipal hospitals deliveries are usually made by the house staff doctors, who are available at all times.

Accordingly, over 250,000 live births in the general municipal hospitals (except one with very few births) were counted, in the manner previously described (for the 13 month study), for each day from Jan. 8, 1948, to Jan. 26, 1957, inclusive (3,307 days or 112 cycles); the first 100 cycles (2,953 days) ended with Feb. 7, 1956. The study began with 1948, as this was the first year with data in fairly convenient form, i.e., names of newborn infants for each day by individual hospital, filed with the Health Department.

Again the sum total of births for the 3 day period, centered at new moon day (days -1, 0, 1), was the lowest of any 3 consecutive days, while the highest 3 day period came virtually half a cycle away on days 13, 14, 15 (i.e., 12.5 to 15.5 days after the average moment of astronomical new moon, the midpoint of day 0). Thus the new moon was associated with the lowest 3 day period, and the full moon was associated with the highest 3 day period, as is evident in Fig. 1. (The average occurrence of full moon is 14.76 or 14.77 days after new moon. Full moon and new moon each last only a moment.) The highest 3 day period exceeded the lowest by 3.4 per cent, after corrections for annual increases in births (3.5 per cent before corrections) during the 112 cycles. All comparisons given will be corrected ones, unless otherwise noted. Generally these corrections have slightly diminished the differences we had actually observed. (Figs. 1, 2, and 3 are based on corrected data.)

The two most different halves of the lunar cycle in regard to birth rate were obtained by dividing the cycle at the beginning of day 13. The dividing line half a cycle away then comes somewhere in day -2. Our designation of days in the lunar cycle had the sequence: -3, -2, -1, 0, 1, 2, 3, 4 . . . 25, 26, day 26 sometimes coinciding with day -3. (The days are numbered in reference to new moon day, which is day 0.) Fig. 1 has been arranged to begin with day -1 (i.e., 1.5 days before the astronomical new moon), as this makes it easier to see the contrast between the most dissimilar halves. The birth rate for the half cycle beginning on day 13 was 1.2 per cent higher

than the other half for the first 100 cycles and 1.1 per cent higher for the 112 cycles. Fig. 1 shows the deviation from the mean birth rate for each day of the cycle in the municipal hospitals for 112 cycles.

Although, according to simple statistical tests commonly employed, the differences noted in the last two paragraphs could occur by chance less than once in 100 times (i.e.,  $p < 0.01$ ), we were not yet reasonably confident that a real difference existed between these most dissimilar halves of the lunar cycle, because these segments had been selected for statistical analysis after their extreme dissimilarity had been noted. To establish whether the observed difference was real, we undertook a similar study of over 250,000 births for the same 112 lunar cycles at 10 private hospitals. Fig. 2 shows the deviation from the mean birth rate for each day of the lunar month in the private hospitals for 112 cycles. The most dissimilar halves of the cycle in regard to birth rate were obtained if the division was made at the end of day 13. The half cycle beginning at the end of day 13 was 1.8 per cent higher than the other half in the first 100 cycles and over 1.6 per cent higher in the 112 cycles. The finding in both studies that the dividing line between the most dissimilar halves came somewhere in day 13 (i.e., 12.5 to 13.5) and that the difference was roughly of the same magnitude strengthened the view that this was a real difference. For the private hospitals, the difference just noted could occur by chance less than once in 10,000 times (i.e.,  $p < 0.0001$ ).

For both hospital groups combined, the difference between the most dissimilar halves (judged by a chi-square test with one degree of freedom) could occur by chance about once in a million times (for 112 cycles and for the first 100 cycles); more conservatively, as there are about 30 days or points for dividing the cycle in half (about 30 possible halves), the above difference could occur by chance about once in 30,000 times (a million divided by 30), i.e.,  $p < 0.0001$ . Fig. 3 depicts the deviation from the mean birth rate for each day of the lunar month during 112 cycles for the combined data, representing over 510,000 births. The data of Figs. 1 and 2 are combined in Fig. 3; more precisely, the municipal hospitals had over 253,000 births, and the private hospitals over 257,000 births, in the 112 cycles. For the combined data, the birth rate in the half cycle beginning on day 13 (here at 13.26) is 1.35 per cent higher than in the other half for 112 cycles and 1.49 per cent higher for the first 100 cycles.

For the combined study (Fig. 3), day 14 appears to deviate to an extraordinary extent above the mean (for 112 cycles). Such a deviation could occur by chance once in 3,000 to 4,000 times, but since there are about 30 days in the lunar cycle, one day can be expected to deviate to an extent that might occur once in 30 times. Applying a correction by dividing 3,000 or 4,000 by 30, we arrive at an estimate indicating that the deviation of day 14 is equivalent to one that could occur by chance less than once in 100 times in a situation having "one degree of freedom" (i.e.,  $p < 0.01$ ).

If no selection of days or segments is made and if a chi-square test is done on the deviations of the 29 or 30 days of the lunar cycle (i.e., 28 or 29 degrees of freedom), a chi-square value greater than 50 is obtained, indicating that such a combination of deviations could occur by chance less than once in 100 times (i.e.,  $p < 0.01$ ) in this study of the combined data for 112 cycles or for the first 100 cycles.

If one visually divides Fig. 3 in half, it will immediately be evident that the first half (day -1 to day 13 at 13.26) has only about 2 days (day 8 and day 13) above average and 13 days below average. In the second half of Fig. 3, the general situation is reversed with only day 16 and day 25 below average while all the other days are above average in birth rate. Even "he that runs may read" this "sign" test (i.e., + or -).



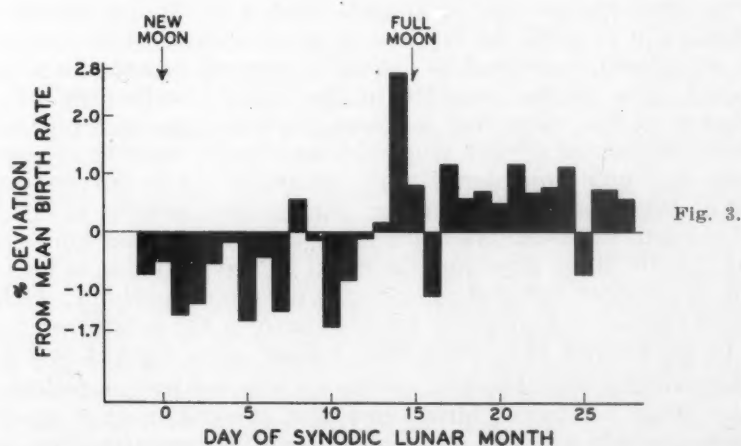
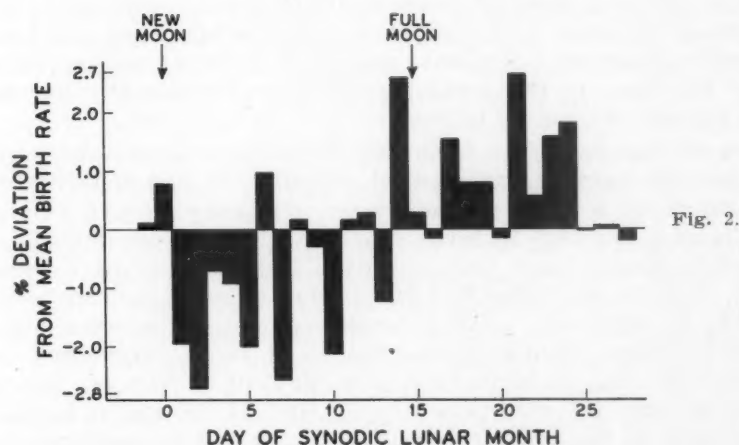
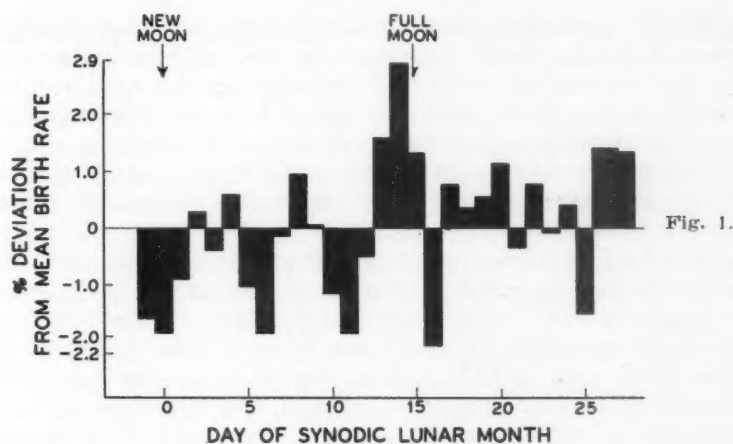


Fig. 1.—Bar graph showing for each day of the synodic lunar month the percentage deviation from the mean birth rate (based on over 250,000 births for 112 cycles) at municipal hospitals.

Fig. 2.—Bar graph showing for each day of the synodic lunar month the percentage deviation from the mean birth rate (based on over 250,000 births for 112 cycles) at 10 private hospitals.

Fig. 3.—Bar graph showing for each day of the synodic lunar month the percentage deviation from the mean birth rate (based on over 510,000 births for 112 cycles) at both the municipal and private hospitals noted in Figs. 1 and 2.



The evidence presented here shows a small but statistically significant synodic lunar (or sun-moon) influence on the human birth rate, and presumably on the conception rate and, perhaps, on the ovulation rate. These rates (or at least the birth rate) are about 1 to 1.5 per cent higher during the half cycle beginning a day or two before full moon as compared to the half cycle beginning a day or two before new moon. In New York City this amounts to an average of 1,000 more births annually during the half cycle starting shortly before full moon.

The peak of conception and probably ovulation appears to occur at full moon or a day before it, judging from the peak of the birth rate, which occurs rather precisely  $9.00 \pm 0.01$  lunar months later. There may be a minimum reached for these processes at about the time of new moon, as indicated by the minimum birth rate at this part of the cycle at the municipal hospitals. The lunar cycle of births, as seen in Figs. 1 and 3, seems to be a prototype of the human ovulatory or menstrual cycle, with new moon being associated with decreased ovulation (and conception) and increased menstrual bleeding, as suggested by the menstrual studies of Gunn and associates,<sup>4</sup> and full moon with increased ovulation and conception. (Although Gunn and his co-workers had suggestive evidence for a lunar influence on menstruation, their data were insufficient for them to put forth a positive or statistically documented conclusion in support of such an influence.)

The rapid rise in births from day 12 to day 14, followed by the sharp drop to day 16, suggests the initial stimulation and activity of excitable tissue followed by a brief refractory or relaxation period. Because of the drop of almost 4 per cent in birth rate in 48 hours from day 14 to day 16, it will be well to obtain more data on days 14, 15, and 16 (and the day before, the day of, and the day after full moon when they do not, respectively, occur on days 14, 15, and 16). The average moment of astronomical full moon occurs between days 14 and 16—on day 15 at 14.765 days after astronomical new moon. The rise in birth rate from day 10 to day 14, followed by the rapid drop to day 16, with recovery on day 17, seems to be the most fascinating quarter of the cycle in regard to births and conceptions, and it merits further watching.

Various physiological, psychological, and pathological phenomena might well be studied in relation to lunar and other cycles. For example, is there any lunar periodicity in regard to deaths in general or attacks of any diseases in particular? The Nobel laureate in chemistry, Arrhenius,<sup>6</sup> presented evidence in favor of the view that various physiological and pathological phenomena were influenced by the tropical lunar cycle (among others), although his data are not now considered very accurate. It is interesting that it is 10.00 tropical lunar or sidereal lunar (star-moon) months to birth from the midpoint between our postulated onset of the last menses and ovulation (or conception), i.e., 10.00 of these months equal 9.25 synodic lunar months or 273.2 days. This is another interesting coincidence—one, perhaps, with anthropocentric implications. (A sidereal lunar month is the length of time it takes the moon to go around the earth with respect to a distant or "fixed" star.)

It is noteworthy that Darwin<sup>7</sup> wrote on this subject as follows: "Man is subject, like other mammals, birds, and even insects, to that mysterious law, which causes certain normal processes, such as gestation, as well as the maturation and duration of various diseases, to follow lunar periods." (He did not present precise quantitative data to support this statement.) Other biologists<sup>4, 8, 9</sup> have pointed to apparently well-documented instances of mating behavior in some species being markedly influenced by the phases of the moon; certain species reach a maximum in mating activity at full moon. This suggests that some of the increase in conceptions (and perhaps ovulations)

in our own species at full moon may be due to an increase in mating activity at this time. Of course, in the human species, this increase is rather small. If there were a marked influence of the synodic lunar cycle on the human birth rate, this would probably have been clearly demonstrated long ago. Because the lunar influence is not of great magnitude in its effect on the human birth rate, it has required so large a sample of births to demonstrate this geophysical influence. It is, therefore, not surprising that a recent report, with less than one-fiftieth of the data that we present for each of the only 2 days of the month (new moon and full moon) considered in that report,<sup>10</sup> failed to find any evidence of a lunar influence on the human birth rate.

The role of the moon (and sun) in the production of tides of the sea is well known. A. A. Michelson,<sup>11</sup> America's first Nobel laureate in science, demonstrated that there is also a land tide, amounting to several inches, due—like the tides of the sea—to the gravitational effect of the moon (and sun) on the solid earth or land. As our bodies are about two-thirds "sea" and one-third "land," we must sustain "tidal" effects. The relative influence (on vital processes) of fluctuations in gravitational fields, light intensity, and any other factors that vary with the synodic lunar and other cycles has yet to be determined. If circumstances permit, the data already collected by us will be used to study the birth rate in relation to other cycles. The day of geophysical biology and medicine is at hand. What may appear of merely theoretical interest in this field today may have considerable practical value tomorrow.

As to immediate practical application of our data, one is tempted to advise that, where conception is desired, the most auspicious time seems to be a day before full moon or day 14 and also full-moon day (but not the day after full moon). The period from day 17 through day 24 of the lunar month also seems rather favorable to conception. When enough data are finally gathered on the effect of the lunar cycle on menstruation, it may be possible to indicate when a nonmenstruating woman is most likely to conceive in relation to the lunar cycle. In other words, we are not yet certain whether or not the rate of conception is essentially a reciprocal of the rate of menstruation at any given time of the lunar month, and our present data only indicate the likelihood of conception on any given day for all women combined (both menstruating and nonmenstruating). Our data and that of Gunn and collaborators<sup>4</sup> suggest that the optimum time for the induction of menstrual bleeding might be from shortly before new moon to about a week (or possibly to day 10) thereafter.

It is interesting that the length of pregnancy can conveniently be measured in weeks—38 weeks from conception and 40 weeks from the onset of the last menses. It is noteworthy that all the lunar guideposts here postulated for important events in human gestation fall on the same day of the week when we plot a continuous course of these events from the onset of the last menses to birth. The time schedule is: (A) onset of last menses (at 0.0 day) at the beginning of the first day; (B) "mid-point" between (A) and (C), marking 10.00 sidereal or tropical months or  $9\frac{1}{4}$  synodic months (273.2 days) before birth, on the 8th day (at 7.3 to 7.4 days); (C) ovulation and conception on the 15th day (at 14.7 to 14.8 days); (D) birth on the 281st day (at 280.5 days). Birth (D) thus occurs on the same day of the week as events (A), (B), and (C) had occurred, respectively, 40, 39, and 38 weeks earlier. These four events cannot all fall on the same day of the week if the week has any other length than 7 days. The moments of completion of each of the first 8 synodic months, counted from the time of conception (C), always fail to fall on the same day of the week as events (A),

(B), (C), and (D). The same failure also occurs with the moments of completion of each of the first 9 sidereal or tropical months, counted from the "mid-point" (B).

From the foregoing, it seems that, on the average, the creation of a human being is completed on the same day of the week that it began. One is, indeed, tempted to remark that the week, the month, and human creation seem to fit into an integrated scheme of things, wherein they are harmoniously interrelated. Such numbers as 7, 9, and 10 are reputedly favorites in mystical systems, and we find them here along with 38, 39, and 40, which are "built" of 9s and 10s. The 19 year Metonic cycle of 235 synodic lunar months (employed in a number of calendars, including the Jewish one) also suggests 9 plus 10, or  $9\frac{1}{2}$  plus  $9\frac{1}{2}$ . The usefulness of the 28 day fictitious "lunar" month may be based on its being a multiple of 7 days (4 weeks).

It should be emphasized that we were originally drawn into this study by the coincidence of 9 mean synodic lunar months equaling (to the nearest whole-numbered day) the mean length of human pregnancy from conception to birth.<sup>1</sup> This observation and the data showing that the mean menstrual cycle is 1.00 mean synodic month in length<sup>3, 4</sup> and that the mean length of pregnancy from the onset of the last menses is 9.500 mean synodic months<sup>5</sup> constitute a combination of coincidences that points to the synodic lunar month as the time unit of the human sexual or reproductive cycle, i.e., the time unit of human reproduction and prenatal development. Indeed, it may be the unit of biological time throughout life in the human and perhaps other species. This fundamental and fascinating hypothesis may well be amenable to experimental study and verification, because the synodic lunar month has a range of variation exceeding 12 hours (i.e.,  $\pm 6$  hours). This is almost  $\pm 0.01$  of a month or over  $\pm 0.25$  of a day. If a study of a sufficiently large sample of women showed that the mean menstrual cycle was longer when the length of the concurrent synodic lunar month was longer than the mean of 29.53 days (and shorter when the concurrent lunar month was shorter), it would indicate that the physical and chemical reactions of the human sexual or reproductive cycle follow or parallel synodic lunar time (the revolution of the moon around the earth with respect to the sun). Likewise, 9 and  $9\frac{1}{2}$  consecutive synodic lunar months are sometimes over half a day longer or shorter than their respective means of 265.8 and 280.5 days. If pregnancies were found to be longer when the concurrent 9 and  $9\frac{1}{2}$  months were longer (and shorter when the concurrent months were shorter), this would indicate that the physical and chemical reactions involved in human metabolism, growth, and development, at least before birth, follow or parallel synodic lunar time. In contrast, the physical and chemical reactions of nonliving things (or matter) follow sidereal time (the rotation of the earth on its axis with reference to the stars). The swing of a pendulum, the physical vibrations of nonliving matter (e.g., atomic vibrations, utilized in atomic clocks), the disintegration of radioactive or unstable atomic nuclei, and presumably the ordinary chemical reactions of nonliving things—all these follow or parallel sidereal time. If it is eventually demonstrated that the physical and chemical reactions or activities of living things (or at least of mankind) follow a different astronomical clock than do these reactions or activities in nonliving things, it will be a finding of profound philosophical as well as scientific import.

The realization that biological processes may follow synodic lunar time might cause some investigators to pause before concluding that some cells or organisms have "built-in clocks" because their activities do not follow or parallel the rotation of the earth on its axis with reference to the sun or the stars (respectively solar or sidereal time).



Even if it were found that the length of pregnancy and of the menstrual cycle did not vary with the small changes in length of the concurrent synodic lunar cycles, the data on births in this paper demonstrate an association of the synodic lunar and human reproductive cycles. Biological and medical scientists, especially in countries where the lunar month is not used in the official calendar, would take a step forward in scientific thinking and teaching if they abandoned the use of the fictitious 28 day "lunar" month and if they adopted the view that human gestation is  $9.00 \pm 0.01$  synodic lunar months from conception (or ovulation) and  $9.50 \pm 0.01$  such months from the onset of the last menstrual period and that the ovulatory or menstrual cycle is  $1.00 \pm 0.01$  such month in length; they might also note that it is  $10.00 \pm 0.01$  sidereal lunar (or tropical lunar) months to birth from the mid-point between the onset of the last menstrual period and ovulation (or conception).

The remarkable agreement of data from various parts of the world in regard to the mean duration of pregnancy, which can be expressed so well in simple or integral numbers of astronomical (lunar) units, strongly suggests that the duration is fixed by or synchronized with astronomical (lunar) cycles. It even suggests the existence of "quanta" of biological time.

The small differences in birth rate described in this paper may appear to be of more interest and usefulness to a biophysicist or a physical biologist than to a "practical clinician," but even the latter may find that repeatedly utilizing a small natural advantage can pay handsome dividends in some cases where increased fertility is desired. Indeed, such utilization may prove to be "the straw that breaks the camel's back." Learned discussions of very small changes (smaller differences than those observed here) in the male: female sex ratio of births appear in scientific periodicals. So it may be apropos to suggest that the influence of the synodic month on the male: female birth ratio might be studied, partly because of old beliefs on the subject. The course of scientific progress has been greatly influenced by discoveries of small differences. It was the bending of light through only 1.7 seconds of arc (less than  $1/100,000$  of a right angle) by the sun's gravitational field that indicated the correctness of Einstein's theory of relativity. And it is the small differences that may be found in the length of menstrual cycles and pregnancies, in relation to concurrent lunar cycles, that may enable further light to be shed on differences in fundamental qualities between living and nonliving things.

In this year 1958, marking the three hundred and fiftieth anniversary of the Dutch discovery of the telescope and the sixtieth anniversary of Arrhenius' paper on cosmic influences in biological processes, we look back on the year that marked the launching of the first man-made "moon" as well as the tercentenary of Harvey's death. We also look forward to next year which will mark the centenary of both the birth of Arrhenius and the publication of Darwin's *The Origin of Species*. So it may be appropriate, in this first International Geophysical Year, to pause and consider our relation in time, as well as in space, to the astronomical universe about us, and perhaps to ponder the thought that our hearts and cells or at least the hearts and cells of our unborn may keep time with a different clock in the sky than does the pendulum or "ticker" of the clock "over there on the mantelpiece" or "Big Ben" in London.

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## ERROR IN REPORTED DATE OF LAST MENSTRUAL PERIOD

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THE predetermination of the expected date of confinement has more than social convenience as a basis. The sequential evaluation of fundal growth (a reflection of fetal well-being) and the selection of the date for elective repeat cesarean section (to avoid iatrogenic prematurity) are but two examples of the medical value of this calculation. Accordingly, it might be Pertinent to Comment on the commonest technique used for measuring the "EDC," namely the "LMP."

The practice of determining the expected date of confinement from the first day of the last menstrual period is recognized to be at its best only an approximation. The causes for deviations from the computed confinement date are numerous but for simplicity may be thought of as (1) biological variation; (2) variation due to pathological conditions; and (3) reporting error due to the failure of the patient to recall the exact date of the first day of her last menstrual period. It is with this last component of variation that this comment is concerned. The purpose here is to describe, by means of indirect evidence, one type of error that occurs when patients are asked to recall the date of the first day of their last menstrual period.

### Date of Last Menstrual Period

It seems reasonable to hypothesize that in a large series of cases the actual dates of the first day of the last menstrual period would occur with approximately equal frequency for the 28 dates common to all months. Thus, in this large series a certain number of women (1/28 of the total) would be expected to report the first of the month as the first day of their last menstrual period. An equal number would be expected to report the 2nd day, 3rd day, and so on up to and including the 28th day. Since the remaining dates are not common to all months they would occur less frequently. For this reason the 29th, 30th, and 31st days of the month have been excluded in this study.

To test the extent of agreement between the number of cases expected for each day of the month and the actual number observed, a sample of 872 histories of women who were delivered at The Johns Hopkins Hospital during the period 1953-1955 was selected. From these, the cases with an unknown LMP or an LMP on the 29th, 30th, or 31st day were discarded. The remaining sample was subdivided into three groups: white private patients (238

cases); white ward patients (174 cases), and Negro ward (371 cases). The distributions of these dates of LMP along with the number expected for each date are shown in Fig. 1.

Among the white private patients it is apparent that the 1st, 10th, and the 25th days of the month were more frequently reported as the LMP than were any of the other days. For the white ward patients this was not the case. In this group there was a slight preference for the 27th and 28th days of the month. For Negro ward cases the 1st, 15th, 20th, 25th, and 28th days were preferred. Of the three groups studied, the dates given by white ward patients were most evenly distributed throughout the days of the month.

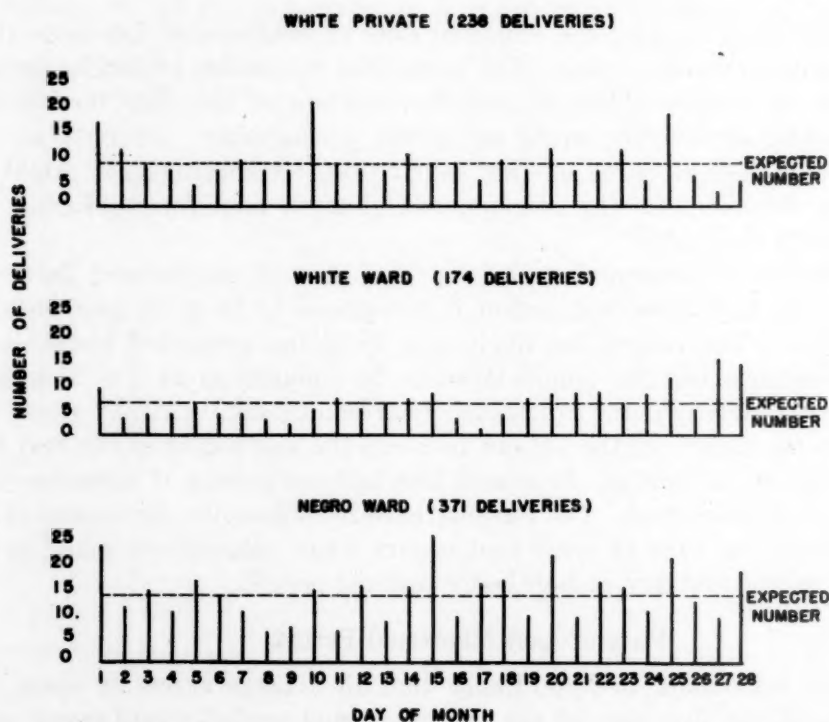


Fig. 1.—Reported date of last menstrual period for obstetrical patients delivered at The Johns Hopkins Hospital, 1953-1955.

The evidence of a systematic distribution of the dates of last menstrual periods for obstetrical patients in one hospital suggested an extension of the study population to find out whether this occurred in other obstetrical services. The certificate of live birth used by the Baltimore City Health Department has an item that asks for this date. Thus, it was possible to get the frequency distribution of LMP dates from a sample of births that occurred in the city's obstetrical services. Fig. 2 shows this distribution by race for a sample of 944 births registered in 1957. The records of white and Negro both show a greater frequency of certain dates. For the white the most frequently reported dates were the 1st, 4th, 10th, 15th, 20th, and 25th. Among the non-white the 15th was by far the most frequently reported date. Other preferred dates included the 1st, 10th, and 20th.

As a generalization, the combined data representing 1,727 cases (Fig. 3), the indications are that in the reporting of the first day of the last menstrual period there is a bias favoring the 1st and 15th days of the month and to a

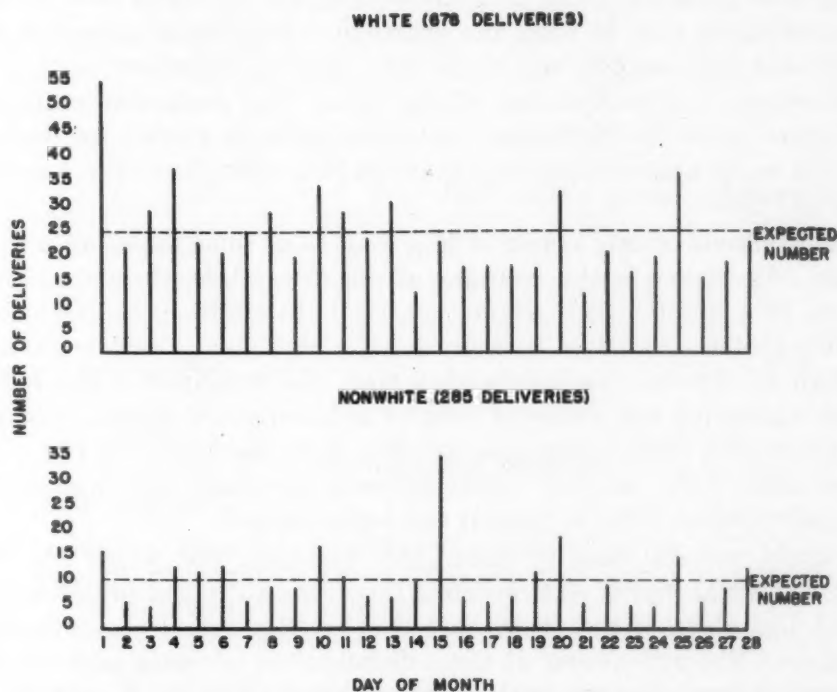


Fig. 2.—Reported date of last menstrual period for obstetrical patients delivered in hospitals in Baltimore, Maryland, 1957.

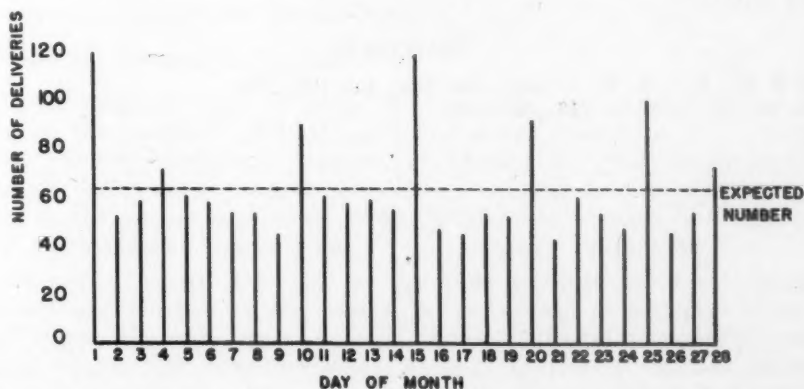


Fig. 3.—Reported date of last menstrual period for 1,727 obstetrical patients delivered in hospitals in Baltimore, Maryland, 1953-1957.

smaller extent the 10th, 20th, and 25th days. Thus, these 5 days which together constitute only about 18 per cent of the 28 dates studied account for almost 30 per cent of the reported dates of LMP.

### Implications

It has frequently been shown that people develop a preference for certain numbers. For example, Gruber<sup>1</sup> found that when people are asked to



pick any number between 1 and 10, the numbers 7, 3, and 5 were the most frequent selections. Another example of an extreme bias for a particular number, i.e., the 40 week gestation, was pointed out by Taback<sup>2</sup> in reference to the length of gestation. The bias observed in the reporting date of LMP gives a quantitative view of what the practicing obstetrician suspected, that is, that patients frequently do not recall the event and therefore make a convenient selection or approximation of the date. The particular pattern of the LMP dates gives the impression that these patients choose the first day of the month or an approximate date rounded to a multiple of five, i.e., 10th, 15th, 20th, and 25th.

The implications of this source of bias may be of some importance to the obstetrician. For example, the accuracy of this date might affect the clinical management of a questionably postmature case. In addition, the knowledge of these date preferences might be cause for the physician to review the manner in which he obtains this information from his patients. If the patient hesitates in answering the query of date of last menstrual period, a helpful suggestion from the obstetrician such as "Was it in the middle of the month or the first part of the month?" might actually encourage this type of bias and ultimately mislead both the patient and her physician.

This study reveals that, of the 1,727 deliveries for which the date of the last menstrual period was reported, there was a decided preference for the 1st and 15th days of the month and to a smaller extent the 10th, 20th, and 25th days. The appearance of these distributions of dates suggests that lacking precise information the patient, either on her own or perhaps with the assistance of leading questions from her obstetrician, arrives at one of these preferred dates.

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## *Reviews and Abstracts*

EDITED BY LOUIS M. HELLMAN, M.D.

### SELECTED ABSTRACTS

#### **Fertility and Sterility**

*Vol. 9, March-April, 1958.*

- \*Bos, C., and Cleghorn, R. A.: Psychogenic Sterility, p. 84.
- \*Noyes, R. W., Yamate, A. M., and Clewe, T. H.: Ovarian Transplants to the Anterior Chamber of the Eye, p. 99.
- \*Kihlstrom, J. E.: Effect of Artificial Light Upon Male Sperm Antiagglutin Production, p. 114.
- \*Peters, H., Israel, S., and Purshottam, M.: Lactation Period in Indian Women: Duration of Amenorrhea and Vaginal and Cervical Cytology, p. 134.
- \*Jefferies, W. McK., Weir, W. C., Weir, D. R., and Prouty, R. L.: The Use of Cortisone and Related Steroids in Infertility, p. 145.

#### **Bos and Cleghorn: Psychogenic Sterility, p. 84.**

Dissimilar emotions, such as anger, fear, or guilt, may induce similar physiologic effects. Thus, the sustained inhibition of ovulation, manifested as amenorrhea, may be precipitated by new situations, dramatic experiences, or great emotional upheavals. Suppression of ovulation, although recognized as a cause of sterility, occurs with relative infrequency in the general population. When it does take place, it is designated as psychogenic or "hypothalamic" amenorrhea.

Reproductive capacity may also be disturbed when the emotions interfere with normal physiologic function of the vagina, cervix, uterus, or Fallopian tubes. This is seen frequently in the tubal spasm induced by insufflation or attempted salpingography. The authors suggest that unfulfilled sexual desires, by creating vascular congestion and hyperemia, may be more injurious to reproductive function than absolute frigidity.

In regard to the personality factors of sterility patients, it is contended that there are fundamentally two basic attitudes—fear of impregnation and rejection of pregnancy. The actual psychological conflicts which give rise to these emotions are legion, being different in each patient. Nevertheless, it is also a fact that some women who reject the female role are not sterile, but on the contrary have a compulsion to produce large families. It must be remembered that the various conflicts involving pregnancy are expressions of total personality disturbances. If a defense mechanism such as sterility is overcome, the patient may succumb to a more serious psychological disability.

PAUL T. TOPKINS

**Noyes, Yamate, and Clewe:** Ovarian Transplants to the Anterior Chamber of the Eye, p. 99.

Inasmuch as mammalian ova undergo rapid maturation just prior to ovulation, fertilization must occur promptly or else degeneration soon takes place. Because of the impossibility of determining the exact time of ovulation, neither freshly ovulated nor ripe follicular ova are readily available for in vitro study. Having developed a technique for successfully transplanting immature ovarian fragments from a black strain into the anterior chamber of the eyes of an immature albino strain of rabbits the authors now report their quantitative observations concerning the relationship of follicular growth to the maturation and fertility of ova.

Verbal and photographic description of the morphologic changes in the ovarian transplants after castration of the recipient animal with subsequent administration of gonadotropic hormones is presented. Data are based on 1,115 intraspecies ovarian transplants. In 463 transplants follicle development was observed daily and the ova were then removed and stained or else the entire transplant was studied in serial sections. In 470 transplants the fertility of the ova was tested. Ovulation was seen in only 14 instances.

The majority of the antrum-containing follicles of the successful grafts are seen to degenerate but new ones form from surviving primordial follicles within 4 days after transplantation. Following castration of the recipient animal the number of follicles which appear is not dependent upon administered gonadotropic hormone. The rate of growth of the follicles, however, is directly related to injection of pregnant mare's gonadotropic serum. In untreated grafts follicular growth lags, whereas in treated cases the follicles increase in volume at approximately the same rate as follicles in the mature ovary in situ. On the other hand, after injection of human chorionic gonadotropic hormone the follicles in transplants do not grow so rapidly or become so large as those developing in ovaries in situ, and ovulation is rare. Nevertheless, meiotic changes in the ovum's nucleus, and cumulus maturation of these ova seem to progress at the normal rate despite their smaller volume. Only 4.5 per cent of ova removed from maturing follicles proved to be fertile, which is only one tenth the fertility rate anticipated on the basis of previous experiments on follicular ova obtained from mature ovaries in situ. Thus, in spite of their great interest in regard to follicular growth, these studies have not disclosed an ideal source of experimental ova.

PAUL T. TOPKINS

**Kihlstrom:** Effect of Artificial Light Upon Male Sperm Antiagglutinin Production, p. 114.

In male and female genital tracts there exist factors which prevent agglutination of spermatozoa. The male sperm antiagglutinin is found in the prostate, in greater amounts during the summer than in the winter. This report is concerned with the effect of artificial light on sperm antiagglutinin production during the winter.

From October through January semen was collected from 6 male albino rabbits by means of an artificial vagina at intervals of from 4 to 7 days. Semen was collected from all animals on the same days. Three rabbits were treated with measured doses of sun lamp light from October 24 to November 25, beginning with irradiation for 1 minute a day and increasing the irradiation by 1 minute a day until 10 minutes a day was given. The semen was rapidly frozen and stored in a refrigerator until analysis was done. At analysis the sperm antiagglutinin adhering to the surfaces of the spermatozoa was released by oxidation with hydrogen peroxide. The sperm cells were then centrifuged at 7,000 g. for 10 minutes and 0.1 ml. of sperm plasma analyzed.

Both the control animals and those treated showed high antiagglutinin concentrations in their semen specimens during the first period, from October 20 to November 25. During the second period, from November 26 to December 23, antiagglutinin concentration was significantly lower. In the third period, from December 24 to January 20 the treated

animals showed increasing concentrations of antiagglutinins in the specimens, significantly higher than those of the second period. During the first two periods antiagglutination concentrations were not appreciably different in the two groups. During the third period, however, the treated animals exhibited significantly higher levels of antiagglutinin in the semen. In addition, the amount of ejaculate increased in the treated animals in the third period, yielding therefore a substantial increase in the absolute amount of antiagglutinin per ejaculate.

Thus, treatment for 2 months with artificial light during the dark season increased the production of sperm antiagglutinin in the rabbit.

PAUL T. TOPKINS

**Peters, Israel, and Purshottam: Lactation Period in Indian Women: Duration of Amenorrhea and Vaginal and Cervical Cytology, p. 134.**

The investigation was made on 272 lactating women attending a birth control clinic in Bombay. The patients, whose average weight was 85 pounds, were on a very poor diet. This fact was possibly related to the late onset of postpartum menstruation. Only one third of these women menstruated by the end of the eighth postpartum month and only one half by the end of the twelfth postpartum month. In the majority of these patients it required 18 months for menstruation to be re-established. The duration of the amenorrhea in this group of women differed markedly from that reported in similar groups in Europe and America. In the vast majority of nursing mothers in India menstruation does not recur by the end of the fourth postpartum month, lactation amenorrhea of a year or more being quite common and in no way impairing subsequent fertility.

Vaginal smears were taken from 73 patients who had not resumed menstruation and from 52 who had experienced one or more periods since giving birth. Atrophic smears were never seen in lactating menstruating women. They were seen in the early months in patients with lactation amenorrhea but in the later months the smears became intermediate or mature in type.

Vaginal and exocervical smears were taken simultaneously from 125 patients. It was observed that maturation occurred earlier in vaginal smears than in exocervical smears, indicating greater responsiveness of the vaginal mucosa to hormone stimulation.

PAUL T. TOPKINS

**Jefferies, et al.: Use of Cortisone and Related Steroids in Infertility, p. 145.**

For the past 5 years the authors have studied the effects of cortisone or hydrocortisone upon ovulation by trying different dosages and varying the schedules of medication. The patients in the present study had amenorrhea, oligomenorrhea, or irregular menstruation. They were unsuccessful in trying to conceive for 18 months even though their husbands had normal semen specimens.

Case reports of 4 patients are given in detail; all were delivered at term. A total of 9 women with ovarian dysfunction have become pregnant on the authors' low-dosage cortisone or hydrocortisone therapy. Pregnancy occurred as early as 4 weeks and as late as 6 months after the beginning of the effective dose. Four patients responded to the first trial of cortisone or hydrocortisone, whereas the other 5 patients responded to different dosages and schedules. Seven patients exhibited mild acne and hirsutism, 3 of these showing elevated 17-ketosteroids.

Preliminary results in 6 infertile males whose wives were found to be normal and whose semen analyses on at least 3 occasions showed fewer than 40 million, usually fewer than 20 million per ml., after 6 months or more of low-dosage cortisone therapy, demonstrated improvement in 4 instances.

PAUL T. TOPKINS



**Irish Journal of Medical Science**

No. 389, May, 1958.

\*Barry, A. P., and Feeney, J. K.: Placenta Previa: A Clinical Survey, p. 216.

**Barry and Feeney: Placenta Previa: A Clinical Survey, p. 216.**

This is a clinical survey of 609 cases of placenta previa treated between 1948 and 1956. Ninety per cent of the cases were under the personal supervision of the authors. The classification of "complete," "partial," "marginal," and "lateral" was based on a 2 or 3 finger dilatation of the internal os. In the 609 cases, 5 mothers were lost, representing a mortality rate of 0.8 per cent. The gross fetal loss was 25 per cent. The free use of soft tissue radiography has proved to be a potent aid to management of the condition which may be diagnosed even before bleeding has occurred. All "radiological" previa must be kept under close observation in hospital.

The authors suggest that in the management of the condition all cases should be divided into three groups:

1. The patient with heavy hemorrhage and the fetus dead or very immature. Such cases can usually be safely treated per vaginam. Cesarean section is advocated even with a dead fetus in certain exceptional cases.
2. The patient admitted with hemorrhage severe enough to require immediate treatment and the fetus more mature. Such a case should be treated by cesarean section unless the fetus is already dead or unless the degree of previa is slight. If the degree of previa is slight a trial of puncture of the membrane is reasonable.
3. The patient admitted with no present bleeding or only a slight loss. Such a case is treated expectantly in the first instance. Subsequent management will depend on the progress.

Expectant treatment is undertaken in order to reduce fetal loss. The longer the mother with placenta previa remains undelivered the longer she remains in danger of hemorrhage. The patient is kept at complete rest in bed until the performance of the controlled examination at 37 to 38 weeks. The patient is not permitted to visit the toilet or bathroom. The cervix is inspected and repeated estimations of the hemoglobin level are performed. The average duration of expected treatment is 6 weeks.

One hundred and sixty-two cases were treated by puncture of the membranes with a fetal loss of just over 20 per cent. At least 8 of the 34 infants could not have been saved by any form of treatment. Seventy-five cases were treated by bringing down a leg with a fetal loss of 73 per cent. The treatment was carried out when the fetus was already dead or deformed or so immature that survival was unlikely and also in a few urgent cases. In 71 cases no active treatment was considered necessary. The fetal loss was 26 per cent.

Vaginal examination in suspected placenta previa should be performed by an experienced person and it is suggested that anesthesia is unnecessary except in the primigravida.

It has been suggested that significant hemorrhage seldom occurs in placenta previa unless provoked by an examination. This has not been the experience of the authors, especially with patients of high parity. Moderate or severe antepartum hemorrhage occurred apparently without provocation in 140 (22.6 per cent) of the cases. Sudden or violent hemorrhage occurred in 32 patients while they were at rest in bed in the hospital. Nevertheless, provided adequate precautions on the lines indicated are taken, the life of the mother is not subjected to increased risk by expectant treatment.

In cesarean section for placenta previa the lower segment operation should be performed. The immediate postoperative and remote obstetrical outlook is prejudiced by classical section. Cesarean section for placenta previa should be performed only by the experienced obstetrician. When the placenta is on the posterior wall the operation may be easy and relatively bloodless. With anterior previa, however, the bleeding may be

heavy and alarming. In the present series cesarean section was performed in 289 cases (46.9 per cent of the total) mainly for third or fourth degree placenta previa. The gross fetal loss was 14 per cent.

Those who perform cesarean section for placenta previa must be prepared for the occasional performance of cesarean hysterectomy. The following were the indications in the 18 cases treated by hysterectomy: (1) placenta accreta, (2) operative bleeding in the multipara, and (3) rupture of the uterus.

The authors conclude that the only active measures likely to be required are simple puncture of the membranes or lower segment cesarean section: Quite a considerable portion of cases will not require active interference at all.

EDWARD SOLOMONS

### **The Journal of the American Medical Association**

*Vol. 167, Aug. 16, 1958.*

\*Dill, L. V., and Chanatry, J.: Effect of Relaxin on Normal Labor, p. 1910.

Norwood, W. D.: Common Sense Approach to the Problem of Genetic Hazard Due to Diagnostic Radiology, p. 1928.

**Dill and Chanatry: Effect of Relaxin on Normal Labor, p. 1910.**

Two preparations of relaxin, a water-soluble substance extracted from the bovine corpus luteum, were compared with a placebo in a series of 47 obstetric patients, as to the various effects on duration of labor, softening of the cervix, and any other possible effects upon the course of the delivery.

In a double-blind experiment the patients selected were those who: (1) had no medical or other complications in their antenatal course, (2) had entered the hospital prior to a dilatation of 5 cm., (3) had a vertex presentation, and (4) had already achieved fetal engagement. Labor was considered to have started only when there was definite evidence of cervical dilatation and was stopped when full dilatation was reached.

Within the limits of the designed experiment it has not been possible to demonstrate the value of relaxin in the shortening of labor, softening of the cervix, or in the speeding up of cervical dilatation.

L. SONDEES

*Vol. 168, Sept. 6, 1958.*

\*DaSilva, Mauricio Martins, Prem, K. A., Johnson, E. A., McKelvey, J. L., and Syverton, J. T.: Response of Pregnant Women and Their Infants to Poliomyelitis Vaccine, p. 1.

**DaSilva, et al.: Response of Pregnant Women and Their Infants to Poliomyelitis Vaccine, p. 1.**

The response of approximately 188 mothers and their infants to immunization with Salk poliomyelitis vaccine was studied by assay of the neutralizing antibodies in serum specimens. Prior to vaccination 65 per cent of the women were incompletely protected by antibodies. After two injections 82 per cent of 133 women showed measurable titers to all three types of poliomyelitis virus. In the cases where successful antibody production occurred the intradermal injection of a slight amount of antigen was found to be as efficacious as larger amounts injected subcutaneously.

Infants born to tested mothers were found to have the same titers of antibodies as their mothers and the half-life of their respective amounts was generally about 5 weeks. It is thereby evident that the duration of passive immunity is related to the level of

acquired antibody at birth. The response of the infants to direct injections of the antigen was found to be inferior to the responses of the mothers. This gives rise to the thought that the response of the infant was secondary and not primary as believed.

From these studies it is concluded that immunization with the Salk vaccine during pregnancy increases maternal protection against poliomyelitis and prolongs the passive immunity of the newborn infant.

L. SONDEERS

*Vol. 168, Oct. 18, 1958.*

\*Hertz, R., Bergenstal, D. M., Lipsett, M. B., Price, E. B., and Hilbish, T. F.: Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women, p. 845.

**Hertz, et al.: Chemotherapy of Choriocarcinoma and Related Trophoblastic Tumors in Women, p. 845.**

Twenty-seven patients were treated with 4-amino-N<sup>10</sup> methyl pteroylglutamic acid (Methotrexate) for trophoblastic disease. The rationale for the use of Methotrexate, a folic acid antagonist, is the high requirement of folic acid in the rapidly growing fetal-maternal tissues. Therapeutic responses were determined by (a) serial x-rays, (b) examination for pelvic, pulmonary, or cerebral involvement, (c) frequent determinations of chorionic gonadotrophic hormone excretion in the urine. The drug was administered in 5 day courses of 10 to 30 mg. given intramuscularly and on occasion by continuous intravenous drip. In 5 patients, 3 of whom had tissue diagnoses of choriocarcinoma, there has been complete remission for from 8 to 29 months; 7 patients experienced partial remissions; and 10 transient remissions. Five patients did not respond at all. Treatment with Methotrexate has several facets of importance. Side effects of the drug, which include stomatitis, rash, leukopenia, enteritis, jaundice, gastrointestinal ulceration, and acute hepatitis (toxic), appear 5 to 7 days after the cessation of administration. Thus, one cannot alleviate toxic symptoms by merely withholding the drug. As with all chemotherapeutic agents there may be initial and acquired resistance. Only one case in the 27 demonstrated initial resistance. All others manifested an initial sensitivity. Others, after varying periods of treatment, developed resistance to Methotrexate. Further therapy under those conditions has proved fruitless, whereas after varying intervals without therapy some sensitivity to the drug returns. Thus at present intermittent therapy will result in more prolonged remissions.

The authors note that although the morbidity and mortality related to the chemotherapy of metastatic trophoblastic disease are high, the significant remissions obtained justify the use of this therapeutic regimen.

L. SONDEERS

### **Journal of Clinical Endocrinology and Metabolism**

*Vol. 18, October, 1958.*

\*Albert, A., and Kelly, S.: Studies on Biologic Characterization of Human Gonadotropins. II. Comparison of HPG and HCG, p. 1067.

\*Cohen, M., Stiefel, M., Reddy, W. J., and Laidlaw, J. C.: The Secretion and Disposition of Cortisol During Pregnancy, p. 1076.

**Albert and Kelly: Studies on Biologic Characterization of Human Gonadotropins. II. Comparison of HPG and HCG, p. 1067.**

The authors carried out six assays for human chorionic gonadotropin (HCG) by the method of simultaneous response of the ovary and uterus of the intact immature rat. The constants of these assays were then compared with similar constants derived from assays of human pituitary gonadotropin (HGP). The dose ratios that integrate gonadotropic action on the ovary and uterus were widely different for HPG and HCG. It was evident

that HCG was six times as effective as HPG in inducing the secretion of estrogen by the ovary. These two human gonadotropins are different in their action and the procedure outlined can be used for their characterization and identification.

J. EDWARD HALL

**Cohen, et al.: Secretion and Disposition of Cortisol During Pregnancy, p. 1076.**

The plasma levels of free 17-hydroxycorticoids have been found to rise progressively during pregnancy. The explanation for this rise has received widespread study. According to these workers, cortisol accounts for about 90 per cent of the plasma free 17-OHCS in pregnant women during the third trimester. Evidence indicates that the placenta and fetal adrenal do not account for the increased maternal cortisol.

The authors conclude that the rise in the level of plasma cortisol during pregnancy is due mainly to a diminished rate of transformation of F to certain of its metabolites and to a greater retention of the hormone within the intravascular compartment.

J. EDWARD HALL

### Journal of Clinical Investigation

*Vol. 37, June, 1958.*

\*Gallagher, T. F., Kappas, A., Hellman, L., Lipsett, M. B., Pearson, O. H., and West, C. D.: Adrenocortical Hyperfunction in "Idiopathic" Hirsutism and the Stein-Leventhal Syndrome, p. 794.

**Gallagher, et. al.: Adrenocortical Hyperfunction in "Idiopathic" Hirsutism and the Stein-Leventhal Syndrome, p. 794.**

Thirteen consecutive women were selected for study, on the sole criterion of hirsutism; 4 of these were later recognized as having the Stein-Leventhal syndrome. The urinary excretions of androsterone and etiocholanolone were found to be above normal levels in every case. In general, there also was an increased excretion of 11-oxygenated metabolites.

When the hirsute women were given cortisone or hydrocortisone, the excretion of androsterone and etiocholanolone fell. The data are consistent with the hypothesis that hyperfunction of the adrenal cortex is related to the hypertrichosis.

LEON C. CHESLEY

*Vol. 37, August, 1958.*

\*Dancis, J. and Shafran, M.: The Origin of Plasma Proteins in the Guinea Pig Fetus, p. 1093.

**Dancis and Shafran: Origin of Plasma Proteins in Guinea Pig Fetus, p. 1093.**

Plasma proteins and individual proteins separated by zone electrophoresis were labeled with  $S^{35}$  or  $I^{131}$  and injected into pregnant guinea pigs. Significant amounts of proteins were transferred from the maternal to the fetal circulation. Several lines of evidence indicate that the proteins were transferred intact: (1) the electrophoretic pattern of labeled proteins in the fetus corresponded to the pattern of proteins injected into the mother, (2) the specific activity of fetal protein fractions was different from that seen when  $S^{35}$  methionine was injected (and incorporated into proteins synthesized by the fetus), (3) labeled plasma protein fractions from chicken blood were injected into the mother and isolated from fetal blood by specific precipitation, (4) placental preparations did not degrade plasma proteins in vitro.

Injection of  $S^{35}$  methionine into the fetus was followed by the appearance of radioactivity in all fractions of fetal plasma proteins except gamma globulin.

LEON C. CHESLEY



*Vol. 37, October, 1958.*

- \*Dancis, J., Money, W. L., Condon, G. P., and Levitz, M.: The Relative Transfer of Estrogens and Their Glucuronides Across the Placenta in the Guinea Pig, p. 1373.

**Dancis, et al.: Relative Transfer of Estrogens and Their Glucuronides Across the Placenta in the Guinea Pig, p. 1373.**

Placentas of guinea pigs were perfused in situ and the perfusate examined for the C<sup>14</sup>-labeled estradiol and estriol, and their glucuronides, that had been injected into the mother. Conversely, the disappearance of these substances, after addition to the perfusate, was followed.

Estradiol could not be found in the fetal placental perfusate, although estriol was rapidly transferred intact from the maternal circulation. The glucuronides were not transferred in significant amounts. In the converse experiment it was found that the estrogens disappeared rapidly from the "fetal" circulation, while the glucuronides did not. Estriol-C-<sup>14</sup> was identified in the maternal circulation, in this experiment. Storage of the estrogens in the placenta was ruled out by the very low radioactivity present in the placenta at the end of the experiment.

LEON C. CHESLEY

**Journal of Obstetrics and Gynaecology of the British Empire**

*Vol. 65, August, 1958.*

- \*Embrey, M. P.: A Simplified Interval Tocograph, p. 529.  
\*Garrett, W. J., and Moir, J. Chassar: Ergot and the Non-pregnant Uterus, p. 583.  
\*Tacchi, Derek: The Role of the Obstetrician in Megaloblastic Anaemia of Pregnancy and the Puerperium, p. 612.

**Embrey: A Simplified Interval Tocograph, p. 529.**

The author describes a new multichannel internal-external tocograph consisting of an intrauterine balloon of some capacity, connected by tubing to a Hydroflex bellows which forms the recording head of the instrument.

The device can record intrauterine pressure changes obtained synchronously from different parts of the uterus and serve as a single-channel recorder prior to and during labor.

RANDALL D. BLOOMFIELD

**Garrett and Moir: Ergot and the Non-Pregnant Uterus, p. 583.**

The effects of ergot preparations on the contractility of the intact nonpregnant uterus at all stages of the menstrual cycle and anovulatory cycles were studied by the intrauterine balloon method. The drugs caused a slight increase in uterine tone in the first half of normal and in anovulatory cycles. In the second half of normal cycles and during menses the drugs produced a uterine spasm similar to that observed with the puerperal uterus. In general, however, it was felt that the pregnant uterus was far more sensitive to these agents. The authors expressed doubt concerning the positive benefits of ergot preparations in the treatment of dysfunctional bleeding.

RANDALL D. BLOOMFIELD

**Tacchi: Role of Obstetrician in Megaloblastic Anaemia of Pregnancy and the Puerperium, p. 612.**

The author presents 52 cases of megaloblastic anemia. The onset generally occurred insidiously between the thirtieth and thirty-seventh weeks of pregnancy and was characterized by anemia, gastrointestinal complaints, circulatory disturbances, and pyrexia. The associated conditions included pre-eclampsia and pyelitis.

A routine hemoglobin determination at the thirty-fourth to the thirty-sixth week was advised. A complete blood count and hematocrit were taken if the hemoglobin was below 10 Gm. per cent. The correct diagnosis was established by bone marrow biopsy.

A good response to treatment was obtained with folic acid and citrovorum factor. Three patients with an unsuccessful response to vitamin B<sub>12</sub> responded favorably to folic acid therapy.

RANDALL D. BLOOMFIELD

### The Lancet

*Vol. 2, Sept. 6, 1958.*

\*Kerr, D. N. S., and Davidson, S.: The Prophylaxis of Iron-Deficiency Anemia in Pregnancy, p. 483.

**Kerr and Davidson: The Prophylaxis of Iron-Deficiency Anemia in Pregnancy, p. 483.**

In order to study the incidence of anemia of pregnancy all patients (except those who had any disease likely to cause anemia and those who were receiving iron at the time of their first visit) who attended the Simpson Memorial Maternity Pavilion in Edinburgh during February and March (end of winter) and August and September (end of summer) in 1955 and 1956 were studied. In all 1,994 patients were examined. Of them 1,071 were seen initially between the first and eleventh weeks of pregnancy. The mean hemoglobin concentration in this group was 13.0 Gm. per 100 ml., although 32 per cent of these women had a hemoglobin concentration less than the mean and in 2 per cent the concentration was less than 10.4 Gm. per 100 ml. In 698 women first seen before the twelfth and twenty-third weeks of pregnancy the mean hemoglobin concentration was 12.4 Gm. per 100 ml. and in 225 women first seen between the twenty-fourth and fortieth weeks of pregnancy the mean was 11.6 Gm. per 100 ml. Of these latter women, 13.7 per cent had hemoglobin lines less than 10.4 Gm. per 100 ml. and in 78 per cent the line was less than 12.6 Gm. per 100 ml. which was found to be the mean concentration in the entire study. No correlation was found between the incidence of anemia and age, parity, or the number of pregnancies within the previous 5 years.

The fall in hemoglobin during the second trimester was observed in 440 patients who did not receive iron, and was found to vary from 5 per cent in patients in whom the initial hemoglobin concentrations were between 10.4 and 10.9 Gm. per 100 ml. to 20 per cent in those whose initial concentrations were between 14.8 and 15.4 Gm. per 100 ml. and this inverse relationship seemed to be almost stationary in nature.

The anemia could be corrected by the administration of iron during the third trimester in 80 per cent of the patients even though the initial mean corpuscular hemoglobin content was normal. There was no difference in the incidence of gastrointestinal symptoms whether the iron was given as ferrous sulfate or gluconate or, in fact, whether the pill was the control containing only lactose.

The dietary intake of 95 women was estimated and found to contain 13 mg. of iron, a little less than the 15 mg. recommended for pregnant women. Curiously, the mean hemoglobin levels were found to be lower at the end of summer than at the end of winter. No dietary cause for this could be detected.

DAVID M. KYDD



## *Items*

### **American Board of Obstetrics and Gynecology**

The next scheduled examinations (Part II), oral and clinical for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 8 through 19, 1959. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I Examinations will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of new and reopened applications for the 1960 examinations is Aug. 1, 1959. Candidates may submit their applications at any time before that date.

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### **Centennial Meeting of Section on Obstetrics and Gynecology, American Medical Association**

The Section on Obstetrics and Gynecology of the American Medical Association will commemorate the one hundredth anniversary of its founding at the next A.M.A. meeting in Atlantic City, June 8-12, 1959. A special program is being arranged including a commemorative luncheon and an address by Mr. Andrew Claye of Leeds, England, President of the Royal College of Obstetricians and Gynaecologists of Great Britain. Also included are panels on "Pelvic Exenteration—Current Status," "Childbirth—Progress in Management," "Ovarian Tumors," and "Rh Disease." Hotel reservation forms for this meeting will appear in the J.A.M.A. or can be obtained from A.M.A. headquarters, 535 North Dearborn Street, Chicago 10, Illinois.